Lewis 09/763,286

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the CAS Roles thesaurus (/RL field) in this file.

=> d que l13
L1          1749 SEA FILE=HCAPLUS MIYATA T?/AU
L2          2274 SEA FILE=HCAPLUS (PERITONE? OR INRAPERITONE?) (5A) (DIALYS? OR
                 DIALYZ? OR (CARBONYL(5A)STRESS?))
L3           345 SEA FILE=HCAPLUS CARBONYL(5A) (TRAP? OR INACTIVAT? OR NEUTRALI?
                 )
L4            46 SEA FILE=HCAPLUS CARBONYL (5A)SCAVENG?
L5          3806 SEA FILE=HCAPLUS BIGUANID?
L6         20617 SEA FILE=HCAPLUS SULFHYDRYL
L7         93027 SEA FILE=HCAPLUS MERCAPTO?
L8          3608 SEA FILE=HCAPLUS AMINOGUANIDINE#
L9          2152 SEA FILE=HCAPLUS PYRIDOXAMIN?
L10        65790 SEA FILE=HCAPLUS HYDRAZIN?
L11           13 SEA FILE=HCAPLUS L1 AND L2
L12           15 SEA FILE=HCAPLUS L2 AND ((L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR
                 L9 OR L10))
L13           24 SEA FILE=HCAPLUS L11 OR L12


=> d ibib abs l13 1-24

L13  ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:625624  HCAPLUS
TITLE:                    Efficient in vitro lowering of carbonyl stress by the
                          glyoxalase system in conventional glucose
                          peritoneal dialysis fluid
AUTHOR(S):                Inagi, Reiko; Miyata, Toshio; Ueda,
                          Yasuhiko; Yoshino, Atsushi; Nangaku, Masaomi; Van
                          Ypersele de Strihou, Charles; Kurokawa, Kiyoshi
CORPORATE SOURCE:         Molecular and Cellular Nephrology, Institute of
                          Medical Sciences and Department of Medicine, Tokai
```

Search completed by David Schreiber  308-4292

University School of Medicine, Kanagawa, Japan
SOURCE: Kidney International (2002), 62(2), 679-687
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background. Reactive carbonyl compds. (RCOs) present in heat-sterilized **peritoneal dialysis** (PD) fluid have been incriminated in the progressive deterioration of the peritoneal membrane obsd. in long-term PD patients. The present study utilized the glyoxalase I (GLO I) system as a new approach to lower in vitro the peritoneal fluid content of RCOs such as methylglyoxal (MGO), glyoxal (GO) and 3-deoxyglucosone (3-DG). GO, MGO, and 3-DG solns. or conventional glucose PD fluids were incubated in vitro with various RCO lowering compds. The evolution of GO, MGO, and 3-DG levels was monitored by high-performance liq. chromatog. The tested compds. included **aminoguanidine** and glutathione (GSH), alone or together with GLO I. The human GLO I gene was overexpressed in Chinese hamster ovary (CHO) cells, or ubiquitously in transgenic mice. Cell supernatant of the CHO transfectant and protein exts. of various organs of the transgenic mice were also tested. **Aminoguanidine** incubated with MGO/GO/3-DG mixts., promptly reduced RCO levels. GSH alone had a similar but milder and slower effect. Together with GLO I, it promptly decreased GO and MGO levels but was less efficient toward 3-DG. After incubation with glucose PD fluid. GSH together with GLO I had the same effect on MGO, GO, and 3-DG levels. Addn. of transfected cell supernatant or tissue exts. overexpressing GLO I, together with GSH to either GO, MGO, or 3-DG solns., promptly and markedly reduced GO and MGO but not 3-DG levels. Conclusions. GLO I together with GSH efficiently lowers glucose-derived RCOs, esp. GO and MGO, both in conventional glucose PD fluids and in RCO solns. The fact that genetically manipulated cells overexpressing GLO I activity have a similar effect suggests that maneuvers raising GLO I activity in peritoneal cells or in the peritoneal cavity might help prevent the deleterious effects of the **peritoneal carbonyl stress** in PD patients. The clin. relevance of this approach is yet to be documented.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:512841 HCAPLUS
DOCUMENT NUMBER: 137:168803

TITLE: Influence of nutritional status on plasma and erythrocyte sulphur amino acids, sulph-hydryls, and inorganic sulphate in end-stage renal disease

AUTHOR(S): Suliman, Mohamed E.; Barany, Peter; Divino Filho, Jose C.; Qureshi, A. Rashid; Stenvinkel, Peter; Heimbuerger, Olof; Anderstam, Bjoern; Lindholm, Bengt; Bergstroem, Jonas
CORPORATE SOURCE: Divisions of Baxter Novum and Renal Medicine, Department of Clinical Science, Karolinska Institutet, Huddinge University Hospital, Stockholm, Swed.

SOURCE: Nephrology, Dialysis, Transplantation (2002), 17(6), 1050-1056
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background. The metab. of sulfur amino acids and sylf-hydryls is altered

in end-stage renal disease (ESRD). Previous studies have focused on the role of vitamin status in the development of hyperhomocysteinemia in such patients, but little information exists about the influence of global nutritional status and hypoalbuminemia on sulfur-contg. compds. in ESRD. As considerable fractions of sulphhydryls in blood are present in erythrocytes (RBC), which among others participate in intra-organ amino acid transport, the relationship between plasma and RBC levels of several of these compds. and various nutritional parameters were evaluated in the present study. Methods. Thirty-seven ESRD patients (24 males, 13 females) on dialysis treatment (18 hemodialysis, 19 continuous ambulatory **peritoneal dialysis**) and 21 healthy subjects (seven males, 14 females) were examd. The subjective global nutritional assessment (SGNA) showed that 10 (27%) patients were malnourished and 27 (73%) had normal nutritional status. Results. All the ESRD patients had high plasma total homocysteine (tHcy) levels. The plasma concns. of methionine (Met) and taurine (Tau) were low, but the levels of the other sulfur-contg. compds. were high. In the RBC, the patients had higher levels of tHcy and Tau than in healthy subjects, but no difference was seen in the concns. of glutathione (GSH), cysteinylglycine (Cys-Gly), Met, and Cys. The plasma inorg. sulfate concns. were 5 times higher in the patients than in healthy subjects, but the levels did not differ significantly between the malnourished patients and those with normal nutritional status. The malnourished patients had lower plasma, but not RBC, levels of tHcy, GSH, and Cys-Gly than those with normal SGNA. Plasma tHcy correlated pos. with serum (s)-albumin and anthropometric parameters and neg. with SGNA. RBC and whole blood, but not plasma, GSH concns. were correlated with hematocrit and were significantly lower in low hematocrit patients (.ltoreq. 37%, n=19) than in those with a high hematocrit (> 37%, n=18). Conclusions. These results show that nutritional status and s-albumin influence plasma, but not RBC, concns. of sylf-hydryls in ESRD patients. This should be considered when the relationships between cardiovascular disease and plasma tHcy or other sulfur-contg. compds. are assessed. The study also shows that GSH concns. in RBC and whole blood are related to hematocrit and not to nutritional parameters, indicating that anemia status rather than nutritional status dets. RBC and whole blood GSH levels in ESRD patients.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:465808 HCAPLUS
DOCUMENT NUMBER: 137:24393
TITLE: Agents for ameliorating carbonyl stress
INVENTOR(S): **Miyata, Toshio**
PATENT ASSIGNEE(S): Kurokawa, Kiyoshi, Japan
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002047677 | A1 | 20020620 | WO 2001-JP10891 | 20011212 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: JP 2000-378112 A 20001212
AB Disclosed are agents for ameliorating carbonyl stress which comprise cysteamine or salts thereof. These agents are usable as drugs directly acting on carbonyl stress by bringing into contact with blood or a **dialyzate** during hemodialysis or **peritoneal dialysis**. These agents, which can be administered via the oral route etc., are also usable as drugs directly acting on carbonyl stress in vivo.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:220422 HCAPLUS
DOCUMENT NUMBER: 136:252544
TITLE: **Peritoneal dialyzates** containing reducing agents or antioxidants
INVENTOR(S): Sakai, Asahi; Nakayama, Masaaki
PATENT ASSIGNEE(S): Japan Science and Technology Corporation, Japan
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002022188 | A1 | 20020321 | WO 2001-JP7772 | 20010907 |

W: CA, CN, KR, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: JP 2000-277810 A 20000913
JP 2001-40718 A 20010216
JP 2001-186642 A 20010620
AB Although glucose has been mainly employed in **peritoneal dialysis** for treating renal failure, there arises a problem that protein undergoes crosslinking due to the oxidn. and denaturation of glucose and thus hardens peritoneal tissue, thereby making it impossible to continue the **peritoneal dialysis**. To overcome this problem, **peritoneal dialyzates** contg. a protein crosslinking inhibitor or an agent dissocg. protein crosslinkage once formed are provided. As the protein crosslinking inhibitor or the agent dissocg. protein crosslinkage once formed, it is effective to use reducing agents or antioxidants. These **peritoneal dialyzates** are prepd. by sterilizing **peritoneal dialyzates** under elevated pressure at high temp. prior to the addn. of the inhibitor(s), then individually sterilizing the inhibitor(s) and adding the same.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:131049 HCAPLUS
DOCUMENT NUMBER: 136:367234
TITLE: Toward better dialysis compatibility: Advances in the

biochemistry and pathophysiology of the peritoneal membranes

AUTHOR(S): **Miyata, Toshio**; Devuyst, Olivier; Kurokawa, Kiyoshi; Van Ypersele De Strihou, Charles

CORPORATE SOURCE: Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan

SOURCE: Kidney International (2002), 61(2), 375-386
CODEN: KDYIA5; ISSN: 0085-2538

PUBLISHER: Blackwell Publishing, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. **Peritoneal dialysis** (PD) has modified our concept of the peritoneal membrane, which is now a topic of active research. Peritoneal solute transport progressively increases with time on PD, enhances the dissipation of the osmotic gradient and, eventually, reduces ultrafiltration capacity. The causes of peritoneal membrane failure remain elusive. Recurrent episodes of peritonitis are not a prerequisite for the development of ultrafiltration failure. Functionally, the changes of the failing peritoneal membrane are best described as an increased functional area of exchange for small solutes between blood and dialyzate. Histol., these events are assocd. with vascular proliferation and structural changes of pre-existing vessels. Gathered evidence, including information on the compn. of peritoneal cavity fluids and its dependence on the uremic environment, have cast a new light on the mol. mechanisms of decline in peritoneal membrane function. Chronic uremia per se modifies the peritoneal membrane and increases the functional area of exchange for small solutes. Biochem. alterations in the peritoneum inherent to uremia might be, at least in part, accounted for by severe reactive carbonyl compds. overload originating both from uremic circulation and PD fluid ("**peritoneal carbonyl stress**"). The mol. events assocd. with long-term PD are similar but more severe than those present in chronic uremia without PD, including modifications of nitric oxide synthase (NOS) and angiogenic growth factors expression, and advanced glycation and lipoxidn. of the peritoneal proteins. This review focuses on reactive carbonyls and their assocn. with a no. of mol. changes obsd. in peritoneal tissues. This hypothetical approach will require further testing. Nevertheless, the insights gained on the peritoneal membrane offer a new paradigm to assess the effect of uremic toxins on serosal membranes. Furthermore, the progress made in the dissection of the mol. events leading to peritoneal membrane failure opens new avenues toward developing safe, more biocompatible **peritoneal dialysis** technologies.

REFERENCE COUNT: 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:751189 HCAPLUS

DOCUMENT NUMBER: 136:261253

TITLE: Chronic uremia induces permeability changes, increased nitric oxide synthase expression, and structural modifications in the peritoneum

AUTHOR(S): Combet, Sophie; Ferrier, Marie-Laure; Van Landschoot, Mieke; Stoenoiu, Maria; Moulin, Pierre; **Miyata, Toshio**; Lameire, Norbert; Devuyst, Olivier

CORPORATE SOURCE: Departments of Nephrology, Universite Catholique de Louvain Medical School, Brussels, B-1200, Belg.

SOURCE: Journal of the American Society of Nephrology (2001), 12(10), 2146-2157
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Advanced glycation end products (AGE), growth factors, and nitric oxide contribute to alterations of the **peritoneum** during **peritoneal dialysis** (PD). These mediators are also involved in chronic uremia, a condition assocd. with increased permeability of serosal membranes. It is unknown whether chronic uremia per se modifies the peritoneum before PD initiation. A rat model of subtotal nephrectomy was used to measure peritoneal permeability after 3, 6, and 9 wk, in parallel with peritoneal nitric oxide synthase (NOS) isoform expression and activity and structural changes. Uremic rats were characterized by a higher peritoneal permeability for small solutes, and an increased NOS activity due to the up-regulation of endothelial and neuronal NOS. The permeability changes and increased NOS activities correlated with the degree of renal failure. Focal areas of vascular proliferation and fibrosis were detected in uremic rats, in relation with a transient up-regulation of vascular endothelial growth factor and basic fibroblast growth factor, as well as vascular deposits of the AGE carboxymethyllysine and pentosidine. Correction of anemia with erythropoietin did not prevent the permeability or structural changes in uremic rats. Thus, in this rat model, uremia induces permeability and structural changes in the peritoneum, in parallel with AGE deposits and up-regulation of specific NOS isoforms and growth factors. These data suggest an independent contribution of uremia in the peritoneal changes during PD and offer a paradigm to better understand the modifications of serosal membranes in uremia.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:713845 HCAPLUS
DOCUMENT NUMBER: 135:251944
TITLE: Isoalloxazine derivatives to neutralize biological contaminants
INVENTOR(S): Platz, Matthew Stewart; Goodrich, Raymond Paul
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. 6,268,120.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2001024781 | A1 | 20010927 | US 2001-777727 | 20010205 |
| US 6268120 | B1 | 20010731 | US 1999-420652 | 19991019 |

PRIORITY APPLN. INFO.: US 1999-420652 A2 19991019
OTHER SOURCE(S): MARPAT 135:251944

AB Methods are provided for neutralization of microorganisms in fluids or on surfaces. Preferably the fluids contain blood or blood products and comprise biol. active proteins. Preferred methods include the steps of adding an activation-effective amt. of a microorganism neutralizer with an isoalloxazine backbone to a fluid and exposing the fluid to a triggering

event. Preferred triggering events include light of a suitable wavelength and intensity to activate the microorganism neutralizer or a pH sufficient to activate the microorganism neutralizer. Other fluids, including juices, water and the like, may also be decontaminated by these methods as may surfaces of foods, animal carcasses, wounds, food prepn. surfaces and bathing and washing vessel surfaces. Compds. with an isoalloxazine backbone are also provided.

L13 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:300555 HCAPLUS
DOCUMENT NUMBER: 134:316078
TITLE: Isoalloxazine derivatives to neutralize biological contaminants
INVENTOR(S): Platz, Matthew Stewart; Goodrich, Raymond Paul, Jr.
PATENT ASSIGNEE(S): Gambro, Inc., USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001028599 | A1 | 20010426 | WO 2000-US25213 | 20000915 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6268120 | B1 | 20010731 | US 1999-420652 | 19991019 |
| EP 1221982 | A1 | 20020717 | EP 2000-965012 | 20000915 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |

PRIORITY APPLN. INFO.: US 1999-420652 A 19991019
WO 2000-US25213 W 20000915
OTHER SOURCE(S): MARPAT 134:316078

AB Methods are provided for neutralization of microorganisms in fluids or on surfaces. Preferably the fluids contain blood or blood products and comprise biol. active proteins. Preferred methods include the steps of adding an activation-effective amt. of a microorganism neutralizer with an isoalloxazine backbone to a fluid and exposing the fluid to a triggering event. Preferred triggering events include light of a suitable wavelength and intensity to activate the microorganism neutralizer or a pH sufficient to activate the microorganism neutralizer. Other fluids, including juices, water and the like, may also be decontaminated by these methods as may surfaces of foods, animal carcasses, wounds, food prepn. surfaces and bathing and washing vessel surfaces. Compds. with an isoalloxazine backbone are also provided. For example, neutralization of microorganisms in blood with 7,8,10-trimethyl,3-sulfonylisoalloxazine (10 .mu.M) and light irradn. was carried out.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2002 ACS

Search completed by David Schreiber 308-4292

ACCESSION NUMBER: 2001:265245 HCAPLUS
DOCUMENT NUMBER: 134:285637
TITLE: Agents for relieving carbonyl stress
INVENTOR(S): **Miyata, Toshio**
PATENT ASSIGNEE(S): Kurokawa, Kiyoshi, Japan
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001024790 | A1 | 20010412 | WO 2000-JP6987 | 20001006 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2000075580 | A5 | 20010510 | AU 2000-75580 | 20001006 |
| EP 1228756 | A1 | 20020807 | EP 2000-964720 | 20001006 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| NO 2002001612 | A | 20020605 | NO 2002-1612 | 20020405 |

PRIORITY APPLN. INFO.: JP 1999-285735 A 19991006
WO 2000-JP6987 W 20001006

AB Agents for relieving carbonyl stress comprise **biguanides**, such as metformin. By administering orally or the like, these agents are usable as drugs directly acting on carbonyl stress in vivo. Immobilized **biguanides** on adsorbents are also used during hemodialysis and **peritoneal dialysis** for the removal of carbonyl compds.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:21042 HCAPLUS
DOCUMENT NUMBER: 135:215950
TITLE: Effect of dwell time on **carbonyl stress** using icodextrin and amino acid **peritoneal dialysis** fluids
AUTHOR(S): Ueda, Yasuhiko; **Miyata, Toshio**; Goffin, Eric; Yoshino, Atsushi; Inagi, Reiko; Ishibashi, Yoshitaka; Izuhara, Yuko; Saito, Akira; Kurokawa, Kiyoshi; Van Ypersele De Strihou, Charles
CORPORATE SOURCE: Molecular and Cellular Nephrology, Tokai University School of Medicine, Kanagawa, Japan
SOURCE: Kidney International (2000), 58(6), 2518-2524
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Deterioration of the peritoneal membrane limits the tech. survival of **peritoneal dialysis** (PD). Advanced glycation of the membrane has been incriminated in this evolution. Advanced glycation end

products (AGEs) develop under the influence of glucose and of its degrdn. products, mainly reactive carbonyl compds. (RCOs) such as glyoxal (GO), methylglyoxal (MGO), and 3-deoxyglucosone (3-DG). The present study was undertaken to evaluate the impact of recently developed glucose-free PD fluids on AGE generation. Recently developed glucose-free PD fluids contg. either icodextrin or amino acids (Nutrineal) were investigated. GO, MGO, and 3-DG [high-performance liq. chromatog. (HPLC)] and total RCOs (spectrophotometry) were measured in fresh solns. and in effluents after various dwell duration. The AGE formation potential of PD fluids and effluents was assessed by incubation at 37.degree.C, for one week, with bovine serum albumin and by the eventual measurement of pentosidine (HPLC) and N.epsilon.-carboxymethyllysine (CML; gas chromatog./mass spectrometry). GO, MGO, and 3-DG ($P < 0.001$) as well as total RCOs levels ($P < 0.01$) were significantly lower in icodextrin and amino acid PD fluid than in com., heat-sterilized, 1.36% glucose PD fluid. Pentosidine and CML generation were also significantly lower ($P < 0.001$) in icodextrin and amino acid PD fluid than in conventional 1.36% glucose PD fluid. The levels of total RCOs, however, increased in icodextrin and amino acid PD fluid effluents with dwell time. AGE formation potential rose accordingly, as demonstrated by a parallel increase in the generation of pentosidine and CML during incubation of PD effluents. The present data demonstrate lower RCO contents and AGE formation potential in fresh icodextrin and amino acid PD fluids than in fresh heat-sterilized glucose PD fluids. However, this difference decreases progressively during dwell time, mainly as a result of the influx of total RCOs.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:716897 HCAPLUS

DOCUMENT NUMBER: 134:216987

TITLE: Mechanism of the inhibitory effect of OPB-9195 [(.+-.)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide] on advanced glycation end product and advanced lipoxidation end product formation

AUTHOR(S): **Miyata, Toshio**; Ueda, Yasuhiko; Asahi, Koichi; Izuhara, Yuko; Inagi, Reiko; Saito, Akira; Van Ypersele De Strihou, Charles; Kurokawa, Kiyoshi

CORPORATE SOURCE: Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, 259-1143, Japan

SOURCE: Journal of the American Society of Nephrology (2000), 11(9), 1719-1725
CODEN: JASNEU; ISSN: 1046-6673

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The accumulation in uremic plasma of reactive carbonyl compds. (RCO) derived from both carbohydrates and lipids ("carbonyl stress") contributes to uremic toxicity by accelerating the advanced glycation and lipoxidn. of proteins. It was previously demonstrated that OPB-9195 [(.+-.)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide] inhibited the in vitro formation of advanced glycation end products (AGE) in uremic plasma. This study was designed to elucidate the mechanism of action of OPB-9195 by further delineating the AGE and advanced lipoxidn. end product (ALE) precursors targeted by this drug. The inhibitory effects of OPB-9195 on the formation of two AGE (N.epsilon.-carboxymethyllysine and pentosidine) on bovine serum albumin incubated

with various AGE precursors were examd. Inhibition of N.epsilon.-carboxymethyllysine and pentosidine formation with OPB-9195 was more efficient than with **aminoguanidine**. OPB-9195 also proved effective in blocking the carbonyl amine chem. processes involved in the formation of two ALE (malondialdehyde-lysine and 4-hydroxynonenal-protein adduct). The efficiency of OPB-9195 was similar to that of **aminoguanidine**. When glucose-based **peritoneal dialysis** fluid was incubated in the presence of OPB-9195, a similar inhibition of AGE formation was obsd. The direct effect of OPB-9195 on major glucose-derived RCO in **peritoneal dialysis** fluids was then evaluated. The effects of OPB-9195 could be accounted for by its ability to trap RCO. The concns. of three major glucose-derived RCO (glyoxal, methylglyoxal, and 3-deoxyglucosone) were significantly lower in the presence of OPB-9195 than in its absence. **Aminoguanidine** had a similar effect. In conclusion, OPB-9195 inhibits both AGE and ALE formation, probably through its ability to trap RCO. OPB-9195 might prove to be a useful tool to inhibit some of the effects of RCO-related uremic toxicity.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:508082 HCAPLUS

DOCUMENT NUMBER: 133:280078

TITLE: Advanced glycation and lipid oxidation of the peritoneal membrane: respective roles of serum and peritoneal fluid reactive carbonyl compounds

AUTHOR(S): **Miyata, Toshio**; Horie, Katsunori; Ueda, Yasuhiko; Fujita, Yuji; Izuhara, Yuko; Hirano, Hiroshi; Uchida, Koji; Saito, Akira; Van Ypersele De Strihou, Charles; Kurokawa, Kiyoshi

CORPORATE SOURCE: Molecular and Cellular Nephrology, Tokai University School of Medicine, Okayama, Japan

SOURCE: Kidney International (2000), 58(1), 425-435
CODEN: KDYIA5; ISSN: 0085-2538

PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Advanced glycation of proteins has been incriminated in the progressive alteration of the **peritoneal** membrane during chronic **peritoneal dialysis** (PD). Advanced glycation end products (AGEs) result from a modification of proteins by reactive carbonyl compds. (RCOs). RCOs resulting from glucose breakdown are present in compd. PD fluid. They also accumulate in uremic plasma. The present study was undertaken to evaluate the resp. contribution of these two sources of RCOs in the genesis of peritoneal AGEs. Three major RCOs formed during heat sterilization of PD fluid, i.e., glyoxal, methylglyoxal, and 3-deoxyglucosone, and total RCOs were measured in compd. PD fluid and in PD effluent. The generation of pentosidine, used as a surrogate marker for AGEs, during one-week incubations of PD fluid and effluent samples fortified with bovine serum albumin (BSA) was measured by high-performance liq. chromatog. Peritoneal samples were stained with antibodies specific for two AGEs derived from carbohydrate-dependent RCOs, NE-(carboxymethyl)lysine (CML) and pentosidine, or for two advanced lipoxidn. end products (ALEs) derived from lipid-dependent RCOs, malondialdehyde (MDA)-lysine and 4-hydroxynonenal (HNE)-protein adduct. Glyoxal, methylglyoxal, and 3-deoxyglucosone were identified in compd. PD fluid. Their levels in PD effluents decreased with dwell time probably by diffusion into blood

circulation. In contrast, the levels of total RCOs were initially low in compd. PD fluid, increased in PD effluent with dwell time probably by diffusion from circulation into the peritoneal cavity, and after 12 h, reached values obsd. in uremic serum. The relevance of the rise in total RCOs for AGE formation is demonstrated by a parallel increase in the generation of pentosidine during incubations of PD effluents. In contrast with RCOs present in glucose-rich PD fluid, RCOs diffusing from uremic circulation originate from both carbohydrates and lipids. Their role in the modification of peritoneal proteins is demonstrated by the immunohistochem. study of peritoneal tissue. Two AGEs and two ALEs increase in parallel in the mesothelial layers and in vascular wall of small arteries in the peritoneum. Protein modification of the peritoneum is detd. not only by RCOs originating in PD fluid, but also by RCOs originating from the uremic circulation. The present data might be relevant to current attempts to improve PD fluid toxicity by lowering its glucose content.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:424391 HCAPLUS
DOCUMENT NUMBER: 133:308659
TITLE: Mechanisms for the formation of glycosidation products in end-stage renal disease
AUTHOR(S): Weiss, Miriam F.; Erhard, Penny; Kader-Attia, Fatma A.; Wu, Yu Ching; DeOreo, Peter B.; Araki, Atsushi; Glomb, Marcus A.; Monnier, Vincent M.
CORPORATE SOURCE: Division of Nephrology, Department of Medicine, University Hospitals of Cleveland, Cleveland, OH, USA
SOURCE: Kidney International (2000), 57(6), 2571-2585
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Advanced glycation end products (AGEs) accumulate on tissue and plasma proteins in patients with renal failure far in excess of normal aging or diabetes. The aim of these studies was to elucidate the nature of the precursors and the pathways that lead to an accelerated formation of 2 structurally identified AGEs [pentosidine and N.epsilon.(carboxymethyl)lysine (CML)] in the uremic milieu. Blood serum levels of the glycosidation. products, pentosidine and CML, were quantitated by HPLC in uremic patients treated by dialysis. The formation of early glycation products (as furosine) and late glycosidation. products was modeled in uremic serum and in spent **peritoneal dialyzate**. Clin. factors that affect circulating levels of AGEs included dialysis clearance and dialyzer membrane pore size, but not the presence or absence of diabetes. Both pentosidine and CML form at an accelerated rate in serum from uremic patients. Chelating agents most effectively slow the formation in vitro. In uremic fluids, the primary mechanism of formation of pentosidine is through the Amadori pathway. The primary mechanism of formation of CML is through metal-chelated autoxidn. of reducing sugars generating reactive carbonyl precursors. In uremic serum, the presence of an unidentified reactive low mol. wt. precursor accelerates the formation of pentosidine. The formation of the 2 glycosidation. products, pentosidine and CML, proceeds by different pathways and is enhanced by different precursors in the uremic milieu. The formation of both AGEs is markedly enhanced by metal-catalyzed reactions, evidence for the presence of increased metal-ion mediated oxidant stress in uremia.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:253862 HCAPLUS
DOCUMENT NUMBER: 133:148688
TITLE: Vascular proliferation and enhanced expression of endothelial nitric oxide synthase in human **peritoneum** exposed to long-term **peritoneal dialysis**
AUTHOR(S): Combet, Sophie; **Miyata, Toshio**; Moulin, Pierre; Pouthier, Dominique; Goffin, Eric; Devuyst, Olivier
CORPORATE SOURCE: Division of Nephrology, Universite Catholique de Louvain Medical School, Brussels, B-1200, Belg.
SOURCE: Journal of the American Society of Nephrology (2000), 11(4), 717-728
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Long-term **peritoneal dialysis** (PD) is assocd. with alterations in peritoneal permeability and loss of ultrafiltration. These changes originate from increased peritoneal surface area, but the morphol. and mol. mechanisms involved remain unknown. The hypothesis that modifications of activity and/or expression of NO synthase (NOS) isoenzymes might play a role in these modifications, via enhanced local prodn. of NO, was tested in this study. NOS activities were measured by the L-citrulline assay in peritoneal biopsies from 7 control subjects, 8 uremic patients immediately before the onset of PD, and 13 uremic patients on short-term (<18 mo, n = 6) or long-term (>18 mo, n = 7) PD. Peritoneal NOS activity is increased 5 -fold in long-term PD patients compared with control subjects. In uremic patients, NOS activity is pos. correlated with the duration of PD. Increased NOS activity is mediated solely by Ca2+-dependent NOS and, as shown by immunoblotting, an upregulation of endothelial NOS. The biol. relevance of increased NOS in long-term PD was demonstrated by enhanced nitrotyrosine immunoreactivity and a significant increase in vascular d. and endothelial area in the peritoneum. Immunoblotting and immunostaining studies demonstrated an upregulation of vascular endothelial growth factor (VEGF) mostly along the endothelium lining peritoneal blood vessels in long-term PD patients. In the latter, VEGF colocalized with the advanced glycation end product pentosidine deposits. These data provide a morphol. (angiogenesis and increased endothelial area) and mol. (enhanced NOS activity and endothelial NOS upregulation) basis for explaining the permeability changes obsd. in long-term PD. They also support the implication of local advanced glycation end product deposits and liberation of VEGF in that process.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:144768 HCAPLUS
DOCUMENT NUMBER: 132:185463
TITLE: Drugs for relieving **carbonyl stress** and **peritoneal dialyzates**
INVENTOR(S): **Miyata, Toshio**
PATENT ASSIGNEE(S): Kurokawa, Kiyoshi, Japan
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000010606 | A1 | 20000302 | WO 1999-JP4521 | 19990823 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9953045 | A1 | 20000314 | AU 1999-53045 | 19990823 |
| EP 1108434 | A1 | 20010620 | EP 1999-938581 | 19990823 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| NO 2001000931 | A | 20010423 | NO 2001-931 | 20010223 |

PRIORITY APPLN. INFO.: JP 1998-237108 A 19980824
JP 1999-155393 A 19990602
WO 1999-JP4521 W 19990823

AB The invention relates to drugs for relieving **carbonyl stress** in the **peritoneal** cavity to be used in **peritoneal dialyzates** which contain **carbonyl** compd.-**trapping** agents as the active ingredient. Carbonyl compds. formed and accumulated during **peritoneal dialysis** are **inactivated** or eliminated by **carbonyl** compd.-**trapping** agents such as **aminoguanidine**. Carbonyl compds. formed during the sterilization and storage of **peritoneal dialyzates** are eliminated by preliminarily bringing into contact with the trapping agents. Further, addn. of the trapping agents to **peritoneal dialyzates** or circulation of the trapping agents by using a cartridge for **trapping carbonyl** compds. makes it possible to eliminate carbonyl compds. originating in the blood of the patients which flow into the **peritoneal** cavity as the **dialysis** proceeds. Thus, modification of proteins in the peritoneal cavity can be inhibited and **peritoneal** damage in assocn. with **peritoneal dialysis** can be relieved.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:84654 HCAPLUS
DOCUMENT NUMBER: 132:141934
TITLE: Method and apparatus for inactivation of biological contaminants using photosensitizers
INVENTOR(S): Goodrich, Raymond Paul, Jr.; Corbin, Frank, Iii; Wood, Edward C., Jr.; Hlavinka, Dennis
PATENT ASSIGNEE(S): Cobe Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

Search completed by David Schreiber 308-4292

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000004930 | A2 | 20000203 | WO 1999-US16404 | 19990721 |
| WO 2000004930 | A3 | 20000817 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6258577 | B1 | 20010710 | US 1998-119666 | 19980721 |
| CA 2304696 | AA | 20000203 | CA 1999-2304696 | 19990721 |
| AU 9952198 | A1 | 20000214 | AU 1999-52198 | 19990721 |
| AU 744978 | B2 | 20020307 | | |
| EP 1047458 | A2 | 20001102 | EP 1999-937340 | 19990721 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9906622 | A | 20011218 | BR 1999-6622 | 19990721 |
| ZA 2000001357 | A | 20001017 | ZA 2000-1357 | 20000316 |
| NO 2000001440 | A | 20000519 | NO 2000-1440 | 20000320 |

PRIORITY APPLN. INFO.:
US 1998-119666 A 19980721
US 1999-357188 A 19990720
WO 1999-US16404 W 19990721

AB Methods and apparatuses are provided for inactivation of microorganisms in fluids or on surfaces. Preferably the fluids contain blood or blood products and comprise biol. active proteins. Preferred methods include the steps of adding an effective, non-toxic amt. of an endogenous photosensitizer to a fluid and exposing the fluid to photoradiation sufficient to activate the endogenous photosensitizer whereby microorganisms are inactivated. Other fluids, including juices, water and the like, may also be decontaminated by these methods as may surfaces of foods, animal carcasses, wounds, food prepn. surfaces and bathing and washing vessel surfaces. Alloxazines and K- and L- vitamins are among the preferred photosensitizers. Systems and apparatuses for flow-through and batch processes are also provided for decontamination of such fluids using photosensitizers.

L13 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:793542 HCAPLUS
DOCUMENT NUMBER: 132:147091
TITLE: Glucose degradation product methylglyoxal enhances the production of vascular endothelial growth factor in peritoneal cells: role in the functional and morphological alterations of **peritoneal** membranes in **peritoneal dialysis**
AUTHOR(S): Inagi, R.; **Miyata, T.**; Yamamoto, T.; Suzuki, D.; Urakami, K.-i.; Saito, A.; van Ypersele de Strihou, C.; Kurokawa, K.
CORPORATE SOURCE: Institute of Medical Sciences, Department of Internal Medicine, Molecular and Cellular Nephrology, Tokai University School of Medicine, Kanagawa, Japan
SOURCE: FEBS Letters (1999), 463(3), 260-264
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.

Search completed by David Schreiber 308-4292

DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Peritoneal** membrane permeability deteriorates in **peritoneal dialysis** (PD) patients. The authors test whether glucose degrdn. products (GDPs) in PD fluids, glyoxal, methylglyoxal and 3-deoxyglucosone, stimulate the prodn. of vascular endothelial growth factor (VEGF), a factor known to enhance vascular permeability and angiogenesis. VEGF increased in cultured rat mesothelial and human endothelial cells exposed to methylglyoxal, but not to glyoxal or 3-deoxyglucosone. VEGF also increased in peritoneal tissue of rats given i.p. methylglyoxal. VEGF and carboxymethyllysine (CML) (formed from GDPs) co-localized immunohistochem. in mesothelial layer and vascular walls of the peritoneal membrane of patients given chronic PD. By contrast, in the peritoneum of non-uremic subjects, VEGF was identified only in vascular walls, in the absence of CML. VEGF prodn. induced by GDPs may play a role in the progressive deterioration of the peritoneal membrane.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:238337 HCAPLUS
DOCUMENT NUMBER: 130:329218
TITLE: Antimicrobial catheters for **peritoneal dialysis**
INVENTOR(S): Tanahashi, Kazuhiro
PATENT ASSIGNEE(S): Toray Industries, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 11099200 | A2 | 19990413 | JP 1997-279911 | 19970926 |

AB Antimicrobial catheters for **peritoneal dialysis** are prepd. from vinyl, acrylic or other polymers and coated with antimicrobial substances such as .beta.-lactam antibiotics and cationic, anionic, amphoteric or nonionic surfactants.

L13 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:212630 HCAPLUS
DOCUMENT NUMBER: 131:53490
TITLE: A sensitive and specific ELISA for plasma pentosidine
AUTHOR(S): Izuhara, Yuko; **Miyata, Toshio**; Ueda, Yasuhiko; Suzuki, Daisuke; Asahi, Koichi; Inagi, Reiko; Sakai, Hideto; Kurokawa, Kiyoshi
CORPORATE SOURCE: Tokai University School of Medicine, Kanagawa, 259-1193, Japan
SOURCE: Nephrology, Dialysis, Transplantation (1999), 14(3), 576-580
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Advanced glycation end products are formed by non-enzymic glycation and oxidn. reaction. Pentosidine is a well-known and characterized structure

among them, and has been implicated in the pathogenesis of complications assocd. with chronic renal failure and long-term dialysis, such as dialysis-related amyloidosis and atherosclerosis. We established a highly sensitive and specific competitive ELISA (ELISA) for plasma pentosidine and applied it to large nos. of plasma samples including hemodialysis (HD) and continuous ambulatory **peritoneal dialysis** (CAPD) patients. We compared their plasma pentosidine levels detd. by the competitive ELISA with those detd. by high-performance liq. chromatog. (HPLC) assay currently used. The plasma pentosidine levels detd. by the ELISA were correlated well with those detd. by sophisticated instrumental HPLC assay, both in non-diabetic and diabetic dialysis patients. Both analyses yielded comparable results, with over 8-fold higher plasma pentosidine levels in HD and CAPD patients, irresp. of the presence or absence of diabetes, as compared to normal subjects and non-uremic diabetic patients. The competitive ELISA will provide a rapid and convenient detn. of plasma pentosidine content and thus be useful to assess the carbonyl stress in uremic patients.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:735879 HCAPLUS
DOCUMENT NUMBER: 128:30710
TITLE: Antibodies to levuglandin E2 (LGE2) protein antigens
INVENTOR(S): Salomon, Robert G.
PATENT ASSIGNEE(S): Case Western Reserve University, USA
SOURCE: U.S., 46 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5686250 | A | 19971111 | US 1996-509180 | 19960731 |

AB Levuglandin (LG) derivs. are used as antigens for raising antibodies useful in diagnostic assays. The antibodies produced by LG-carrier protein adducts can be used to detect adducts of LGE2 with human low-d. lipoprotein (LDL). LGE2-protein adduct immunoreactivity may be generated during in vitro free-radical oxidn. of LDL. An ELISA for detecting adducts of LGE2 with human LDL is also described.

L13 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:212618 HCAPLUS
DOCUMENT NUMBER: 126:262754
TITLE: Clearance of pentosidine, and advanced glycation end product, by different modalities of renal replacement therapy
AUTHOR(S): **Miyata, Toshio**; Ueda, Yasuhiko; Yoshida, Atsuhiro; Sugiyama, Satoshi; Iida, Yoshiyasu; Jadoul, Michel; Maeda, Kenji; Kurokawa, Kiyoshi; Van Ypersele De Strihou, Charles
CORPORATE SOURCE: Department of Internal Medicine, Branch Hospital, Institute of Medical Sciences and Department of Medicine, Nagoya University School of Medicine, Tokai University School of Medicine, Isehara, Japan
SOURCE: Kidney International (1997), 51(3), 880-887
CODEN: KDYIA5; ISSN: 0085-2538

PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors recently demonstrated that pentosidine, an advanced glycation end product, accumulates markedly as albumin-linked form (Palb) and in free-form (Pfree) in the plasma of patients with end-stage renal failure. The present study was undertaken to examine the clearance of Palb and Pfree by different modalities of renal replacement therapy, i.e., hemodialysis (HD), continuous ambulatory **peritoneal dialysis** (CAPD), and renal transplantation. HD cleared Pfree (9.4 nmol/kg/HD) but not Palb, by diffusion but not by membrane adsorption, whereas CAPD cleared both Palb (4.03 nmol/kg/day) and Pfree (2.43 nmol/kg/day). Plasma total pentosidine levels were significantly lower in CAPD (0.97 nmol/mL) than in HD (1.19 nmol/mL), as the result of a lower serum albumin level in the former patients. Indeed, Palb expressed per mg albumin was virtually identical in HD and CAPD. By contrast, Pfree was significantly lower in CAPD than in HD. Palb levels were significantly correlated with plasma Pfree levels in both HD and CAPD patients, but not in the CAPD dialyzate. Pentosidine transport across the peritoneum occurs mainly by diffusion, both as Palb and Pfree. Interestingly, peritoneal Palb clearance (0.17 mL/min) significantly exceeded albumin clearance (0.11 mL/min). Palb levels being significantly higher in the peritoneal fluid (36.28 pmol/mg) than in the serum (27.12 pmol/mg), thus raises the possibility of a facilitated diffusion of Palb or an active transport mechanism for protein-linked pentosidine into the peritoneal cavity. After renal transplantation, plasma Pfree fell rapidly, remained barely detectable after one month, and returned to normal at six months. By contrast, Palb fell more slowly and remained significantly above normal at six months, but returned eventually to normal levels. These findings demonstrate that: (1) both HD and CAPD remove Pfree; (2) the peritoneal clearance of Palb might contribute to the lower level of plasma pentosidine in CAPD than in HD patients; and (3) renal transplantation is the best therapeutic modality to normalize both Palb and Pfree levels.

L13 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:505446 HCAPLUS
DOCUMENT NUMBER: 125:139738
TITLE: Modification of .beta.2m with advanced glycation end products as observed in dialysis-related amyloidosis by 3-DG accumulating in uremic serum
AUTHOR(S): Niwa, Toshimitsu; Katsuzaki, Tomoyuki; Momoi, Tomoko; Miyazaki, Takashi; Ogawa, Hiroshi; Saito, Akira; Miyazaki, Shigeru; Maeda, Kenji; Tatemichi, Noriyuki; Takei, Yoshifumi
CORPORATE SOURCE: Nagoya University Branch Hospital, Nagoya, Japan
SOURCE: Kidney International (1996), 49(3), 861-867
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .beta.2Microglobulin (.beta.2m) isolated from the amyloid deposits in patients with dialysis-related amyloidosis (DRA) has been demonstrated to be modified with advanced glycation end products (AGEs). The authors demonstrated that AGE was localized to amyloid deposits in patients with DRA by immunohistochem. using a monoclonal anti-AGE antibody. To clarify the mechanism of AGE modification of .beta.2m-amyloid, the authors studied the effects of 3-deoxyglucosone (3-DG), a potent protein crosslinking intermediate of the Maillard reaction, on the AGE modification of .beta.2m, and quantified the serum levels of 3-DG in patients undergoing

hemodialysis (HD) and continuous ambulatory **peritoneal dialysis** (CAPD), and undialyzed patients. The serum levels of 3-DG were markedly increased in the dialyzed and undialyzed uremic patients. Although the serum level of 3-DG decreased after HD with a mean redn. rate of 67%, it was still significantly higher than in normal serum. Incubation of .beta.2m with 3-DG at 37.degree. emitted fluorescence characteristic for AGE, and caused AGE modification and dimer formation of .beta.2m as demonstrated by Western blotting using the same monoclonal anti-AGE antibody used for immunohistochem. demonstration of AGE in DRA. The AGE-modified dimer of .beta.2m could be extd. from the amyloid tissue of a patient with DRA. The 3-DG showed more intense and faster reactivity with .beta.2m to form AGE and dimer as compared with glucose, and **aminoguanidine** suppressed the AGE and dimer formation of .beta.2m by 3-DG. In conclusion, 3-DG accumulating in uremic serum may be involved in the AGE modification of .beta.2m-amyloid.

L13 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:422230 HCAPLUS
DOCUMENT NUMBER: 115:22230
TITLE: Use of dimercaptosuccinic acid (DMSA) in treating silicon excess-related disorders in blood, kidney, and brain
INVENTOR(S): Gonick, Harvey Craig; Khalil-Manesh, Farhad; Weiler, Elmar Willibald Johannes
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 388241 | A1 | 19900919 | EP 1990-302905 | 19900319 |
| EP 388241 | B1 | 19950125 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| US 4962127 | A | 19901009 | US 1989-325297 | 19890317 |
| CA 2012091 | AA | 19910913 | CA 1990-2012091 | 19900313 |
| AU 9051325 | A1 | 19901108 | AU 1990-51325 | 19900314 |
| AU 626390 | B2 | 19920730 | | |
| JP 03007219 | A2 | 19910114 | JP 1990-68003 | 19900317 |
| JP 07029917 | B4 | 19950405 | | |
| CA 2012470 | AA | 19910919 | CA 1990-2012470 | 19900319 |
| CA 2012470 | C | 19951107 | | |

PRIORITY APPLN. INFO.: US 1989-325297 A 19890317
AB DMSA may be used to reduce the level of silicon in blood and tissue, thereby reducing blood pressure, improving kidney function, preventing or retarding the progression of chronic renal failure, treating the accumulation of silicon in advanced kidney disease, and/or preventing the onset or improving the current status of dementia and Alzheimer's disease.

L13 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:558753 HCAPLUS
DOCUMENT NUMBER: 113:158753
TITLE: Containers for redox-active electrolytes for the preparation of instant medical solutions
INVENTOR(S): Veech, Richard L.
PATENT ASSIGNEE(S): USA

Search completed by David Schreiber 308-4292

Lewis 09/763,286

SOURCE: U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 810,815, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 4929449 | A | 19900529 | US 1986-940331 | 19861217 |
| CA 1285528 | A1 | 19910702 | CA 1986-525698 | 19861218 |
| US 5200200 | A | 19930406 | US 1990-509182 | 19900416 |

PRIORITY APPLN. INFO.: US 1985-810815 19851220
US 1985-810915 19851220
US 1986-940331 19861217

AB Methods are provided for prepg. just before administration unit doses of therapeutic solns. which contain redox-active unstable and/or diffusable metabolites such as a ketoacid, a SH-contg. amino acid, or CO2. The method involves prepg. and storing an aq. soln. of stable components which may or may not contain CO2. A dry powder comprised of unstable components is also prepd. and stored sep. These sep. component compns. are packaged in individual chambers of a common sealed container, which is so constructed as to permit the opening, by externally applied manual means or the like, of a passageway between the chambers at usage. Thus, a fresh soln. in desired full dosage form is preparable just before administration. Improved container structures for this method are also provided. A soln. (pH 5.5-6.5) was made contg. Na+ 124.9, K+ 4, Ca2+ 1.5, cations 132, Cl- 96, l-lactate anion 33.9, anions 132, and CO2 0-0.5 mmol/L. The soln. (1L) was placed in a plastic bag. Sep., cryst. Na pyruvate, sufficient to provide a 5.1 mmol/L soln., was placed into an adjacent bag. When communication was established between the 2 bags, a redox-balanced Ringer's lactate soln., suitable for i.v. administration, was obtained.

Search completed by David Schreiber 308-4292

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show files
File 155:MEDLINE(R) 1966-2002/Sep W3
File   5:Biosis Previews(R) 1969-2002/Sep W3
         (c) 2002 BIOSIS
File 315:ChemEng & Biotec Abs 1970-2002/Aug
         (c) 2002 DECHEMA
File  10:AGRICOLA 70-2002/Sep
         (c) format only 2002 The Dialog Corporation
File  73:EMBASE 1974-2002/Sep W3
         (c) 2002 Elsevier Science B.V.
?ds

Set     Items   Description
S1       2935   AU=MIYATA T? OR AU=MIYATA, T?
S2          0   INTRAPERITONEAL (5N)CARBONYL(5N)STRESS
S3      39952   PERITONE? (3N) (DIALYS? OR DIALYZ?)
S4        200   CARBONYL(5N) (TRAP? OR INACTIVAT? OR NEUTRALI?)
S5       5668   AMINOGUANIDINE? ?
S6       2282   PYRIDOXAMINE? ?
S7      17002   HYDRAZINE? ?
S8       6066   BIGUANID?
S9      48802   SULFHYDRYL
S10     63495   MERCAPTO?
S11      7068   REDUCING(3N)SUGAR? ?
S12       294   CARBONYL?(5N)STRESS?
S13        46   CARBONYL? (5N) INTRAPERITONE?
S14        68   CARBONYL? AND S3
S15        54   S1 AND S3
S16        32   CARBONYL? AND S15
S17        53   (S12 OR S13 OR S14) AND (S4-S10)
S18        42   CARBONYL (5N)SCAVENG?
S19         3   (S12 OR S13 OR S14) AND S18
S20        78   S16 OR S17 OR S19
S21        44   RD S20 (unique items)
?t 21/7/all

 21/7/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13357865   22108319   PMID: 12113603
  Oxidative stress markers in hepatitis C infected hemodialysis patients.
  Koken Tulay; Serteser Mustafa; Kahraman Ahmet; Gokce Cigdem
  Department of Biochemistry, School of Medicine, Kocatepe University,
Afyon, Turkey. tkoken@aku.edu.tr
  Journal of nephrology (Italy)  May-Jun 2002, 15 (3) p302-7, ISSN
1120-3625  Journal Code: 9012268
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  BACKGROUND: Oxidative stress in hemodialysis (HD) patients or hepatitis C
virus (HCV) infections may be related to increased production of free
radicals. We assessed the effect of HCV infection on the oxidative stress
 markers, malondialdehyde (as TBARS), protein carbonyl content and
protein sulfhydryl groups, in chronic HD patients. METHODS: Twenty HCV
infected patients (9 men and 11 women, age 44.8 +/- 14.3 years) and 10
non-HCV infected patients (6 men and 4 women, age 55.6 +/- 14.3 years)
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receiving regular HD were recruited. The average hemodialysis duration was 30 +/- 8 months for HCV (+) patients and 14 +/- 8 months for HCV (-) patients. Controls consisted of healthy subjects. RESULTS: Serum TBARS and carbonyl content were significantly elevated in HCV(-) patients ($p<0.001$, $p<0.05$) and in HCV(+) patients ($p<0.001$, $p<0.001$) vs. Controls. There was also a significant difference in serum TBARS and carbonyl content between HCV(-) patients and HCV(+) patients ($p<0.001$, $p<0.05$). Serum protein sulfhydryl groups in HCV(-) and HCV(+) patients were the same, but significantly lower than in Controls ($p<0.001$, $p<0.001$). When HCV(+) patients were divided into two sub-groups, one with shorter (13.4 +/- 8 months; n=7) and the other with longer (40.3 +/- 8 months; n=13) duration of HD treatment, no differences were found between subgroups. CONCLUSION: HCV infection may aggravate oxidative stress in HD patients.

Record Date Created: 20020712

21/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13351012 22106745 PMID: 12110033

Efficient in vitro lowering of carbonyl stress by the glyoxalase system in conventional glucose peritoneal dialysis fluid.

Inagi Reiko; Miyata Toshio ; Ueda Yasuhiko; Yoshino Atsushi; Nangaku Masaomi; Van Ypersele De Strihou Charles; Kurokawa Kiyoshi

Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Medicine, Tokai University School of Medicine, Kanagawa, Japan, and Service de Nephrologie, Universite Catholique de Louvain, Brussels, Belgium.

Kidney international (United States) Aug 2002, 62 (2) p679-87, ISSN 0085-2538 Journal Code: 0323470

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Efficient in vitro lowering of carbonyl stress by the glyoxalase system in conventional glucose peritoneal dialysis fluid. BACKGROUND: Reactive carbonyl compounds (RCOs) present in heat-sterilized peritoneal dialysis (PD) fluid have been incriminated in the progressive deterioration of the peritoneal membrane observed in long-term PD patients. The present study utilized the glyoxalase I (GLO I) system as a new approach to lower in vitro the peritoneal fluid content of RCOs such as methylglyoxal (MGO), glyoxal (GO) and 3-deoxyglucosone (3-DG). METHODS: GO, MGO, and 3-DG solutions or conventional glucose PD fluids were incubated in vitro with various RCO lowering compounds. The evolution of GO, MGO, and 3-DG levels was monitored by high-performance liquid chromatography. The tested compounds included aminoguanidine and glutathione (GSH), alone or together with GLO I. The human GLO I gene was overexpressed in Chinese hamster ovary (CHO) cells, or ubiquitously in transgenic mice. Cell supernatant of the CHO transfectant and protein extracts of various organs of the transgenic mice were also tested. RESULTS: Aminoguanidine incubated with MGO/GO/3-DG mixtures, promptly reduced RCO levels. GSH alone had a similar but milder and slower effect. Together with GLO I, it promptly decreased GO and MGO levels but was less efficient toward 3-DG. After incubation with glucose PD fluid, GSH together with GLO I had the same effect on MGO, GO, and 3-DG levels. Addition of transfected cell supernatant or tissue extracts overexpressing GLO I, together with GSH to either GO, MGO, or 3-DG solutions, promptly and markedly reduced GO and MGO

but not 3-DG levels. CONCLUSIONS: GLO I together with GSH efficiently lowers glucose-derived RCOs, especially GO and MGO, both in conventional glucose PD fluids and in RCO solutions. The fact that genetically manipulated cells overexpressing GLO I activity have a similar effect suggests that maneuvers raising GLO I activity in peritoneal cells or in the peritoneal cavity might help prevent the deleterious effects of the peritoneal carbonyl stress in PD patients. The clinical relevance of this approach is yet to be documented.
Record Date Created: 20020711

21/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13276762 21839377 PMID: 11849377
Toward better dialysis compatibility: advances in the biochemistry and pathophysiology of the peritoneal membranes.
Miyata Toshio ; Devuyst Olivier; Kurokawa Kiyoshi; van Ypersele de Strihou Charles
Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan. t-miyata@is.icc.u-tokai.ac.jp
Kidney international (United States) Feb 2002, 61 (2) p375-86, ISSN 0085-2538 Journal Code: 0323470
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Peritoneal dialysis (PD) has modified our concept of the peritoneal membrane, which is now a topic of active research. Peritoneal solute transport progressively increases with time on PD, enhances the dissipation of the osmotic gradient and, eventually, reduces ultrafiltration capacity. The causes of peritoneal membrane failure remain elusive. Recurrent episodes of peritonitis are not a prerequisite for the development of ultrafiltration failure. Functionally, the changes of the failing peritoneal membrane are best described as an increased functional area of exchange for small solutes between blood and dialysate. Histologically, these events are associated with vascular proliferation and structural changes of pre-existing vessels. Gathered evidence, including information on the composition of peritoneal cavity fluids and its dependence on the uremic environment, have cast a new light on the molecular mechanisms of decline in peritoneal membrane function. Chronic uremia per se modifies the peritoneal membrane and increases the functional area of exchange for small solutes. Biochemical alterations in the peritoneum inherent to uremia might be, at least in part, accounted for by severe reactive carbonyl compounds overload originating both from uremic circulation and PD fluid ("peritoneal carbonyl stress"). The molecular events associated with long-term PD are similar but more severe than those present in chronic uremia without PD, including modifications of nitric oxide synthase (NOS) and angiogenic growth factors expression, and advanced glycation and lipoxidation of the peritoneal proteins. This review focuses on reactive carbonyls and their association with a number of molecular changes observed in peritoneal tissues. This hypothetical approach will require further testing. Nevertheless, the insights gained on the peritoneal membrane offer a new paradigm to assess the effect of uremic toxins on serosal membranes. Furthermore, the progresses made in the dissection of the molecular events leading to peritoneal membrane failure open new avenues to develop safe,

more biocompatible peritoneal dialysis technologies. (116 Refs.)
Record Date Created: 20020218

21/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13125746 21986601 PMID: 11991200
Effects of aminoguanidine on lipid and protein oxidation in diabetic rat kidneys.
Gogasyavuz Dilek; Kucukkaya Belgin; Ersoz H Onder; Yalcin A Suha; Emerk Kaya; Akalin Sema
Department of Internal Medicine Section of Endocrinology and Metabolism, School of Medicine, Marmara University, Istanbul Turkey. dyavuz@turk.net
International journal of experimental diabetes research (United States) Apr-Jun 2002, 3 (2) p145-51, ISSN 1560-4284 Journal Code: 100962067
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Nonenzymatic glycation of tissue and plasma proteins may stimulate the production of oxidant and carbonyl stress in diabetes. The aim of this study was to evaluate the effects of aminoguanidine (AG) on lipid peroxidation, protein oxidation and nitric oxide (NO) release in diabetic rat kidneys. After induction of diabetes with streptozotocin, female Wistar rats were divided into 2 groups. Group DAG (n=9) rats were given AG hydrogen carbonate (1 g/L) in drinking water and group D (n=8) was diabetic control rats given only tap water. Group H (n=8) was followed as healthy controls. At the end of an 8 week period, NO release, lipid and protein oxidation were determined in kidney tissues. NO release was significantly lower in diabetic rats compared with healthy controls ($p<0.05$). Lipid peroxidation was significantly high in group D (3.9 +/- 0.3 nmol MDA/g tissue) compared with the group DAG (2.6 0.1 nmol MDA/g tissue, $p<0.01$) and group H (2.4 +/- 0.2 nmol MDA/g tissue). Protein oxidation was significantly higher in diabetics than healthy controls (563.8 +/- 23.9, 655.8 +/- 7.2, 431.5 +/- 8.8 mmol carbonyl / g tissue for group DAG, D and H, respectively, $p< 0.05$). A positive correlation between albuminuria and thiobarbituric acid reactive substance (TBARS) levels ($r= 0.54, p<0.005$) and carbonyl content ($r=0.70$, $p<0.0005$) in kidney homogenate were observed. Although AG treatment had no effect on NO release, it significantly decreased lipid peroxidation in diabetic rat cortices. Consequently increased lipid peroxidation -as well as- protein oxidation could be involved in the pathogenesis of diabetic albuminuria.
Record Date Created: 20020506

21/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13091691 21842819 PMID: 11853687
Identification of alpha-dicarbonyl scavengers for cellular protection against carbonyl stress .
Wondrak Georg T; Cervantes-Laurean Daniel; Roberts Michael J; Qasem Jaber G; Kim Moonsun; Jacobson Elaine L; Jacobson Myron K
Department of Pharmacology and Toxicology, College of Pharmacy, Arizona Cancer Center, University of Arizona, Tucson, AZ 85724, USA.
Biochemical pharmacology (England) Feb 1 2002, 63 (3) p361-73,

ISSN 0006-2952 Journal Code: 0101032
Contract/Grant No.: CA43894; CA; NCI; NS38496; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Tissue deterioration and aging have long been associated with the accumulation of chemically induced protein and DNA damage. Reactive oxygen species (ROS) and reactive carbonyl species (RCS), especially alpha-dicarbonyl compounds, are key mediators of damage caused by oxidative stress, glycation, and UV-irradiation. The toxic effects of ROS are counteracted in vivo by antioxidants and antioxidant enzymes, and the deleterious effects of one RCS, methylglyoxal, are counteracted by a ubiquitous glyoxalase system. Carbonyl stress as a result of toxic effects of various mono-dicarbonyls (e.g. 4-hydroxynonenal) and alpha-dicarbonyls (e.g. glyoxal and deoxyosones) cannot be directly antagonized by antioxidants, and only a small number of biological carbonyl scavengers like glutathione (GSH) have been identified to date. We have developed a new screening method for the identification of carbonyl scavengers using a rapid glycation system that proceeds independent of oxygen and therefore, excludes identification of inhibitory compounds acting as antioxidants. Using this screening assay adapted to 96-well microtiter plates, we have identified the cysteine derivative 3,3-dimethyl-D-cysteine as a potent inhibitor of non-oxidative advanced glycation. Comparative kinetic analyses demonstrated the superior alpha-oxoaldehyde-scavenging activity of D-penicillamine over that of aminoguanidine . D-Penicillamine traps alpha-oxoaldehydes by forming a 2-acylthiazolidine derivative as shown by structure elucidation of reaction products between D-penicillamine and methylglyoxal or phenylglyoxal. We demonstrated that upon co-incubation, D-penicillamine protects human skin keratinocytes and fibroblasts (CF3 cells) against glyoxal- and methylglyoxal-induced carbonyl toxicity. Our research qualifies alpha-amino-beta- mercapto -beta,beta-dimethyl-ethane as a promising pharmacophore for the development of related alpha-dicarbonyl scavengers as therapeutic agents to protect cells against carbonyl stress .

Record Date Created: 20020220

21/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12818220 21395249 PMID: 11503207

Identification of protein carbonyls after two-dimensional electrophoresis.

Conrad C C; Choi J; Malakowsky C A; Talent J M; Dai R; Marshall P; Gracy R W

Molecular Aging Unit, Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Texas, USA.

Proteomics (Germany) Jul 2001, 1 (7) p829-34, ISSN 1615-9853
Journal Code: 101092707
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The oxidative modification of proteins plays a major role in a number of human diseases, but identity of the specific proteins that are most susceptible to oxidation has posed a difficult problem. Protein carbonyls

are increased after oxidative stress , and after derivatization with 2,4-dinitrophenyl hydrazine (DNP) they can be detected by various analytical and immunological methods. Although high resolution two-dimensional electrophoresis (2-DE) can resolve virtually all proteins present in a cell or tissue it has been difficult to determine the oxidized proteins because the DNP-derivatization process alters the isoelectric points of proteins, and additional procedures must be utilized to remove reaction byproducts. These additional procedures can lead to loss of sample, and poor isoelectric resolution on immobilized pH gradient (IPG) strips. We have developed a method that allows the IPG strips to be derivatized with DNP directly following isoelectric focusing of the proteins. This method allows the visualization of oxidized proteins by 2-DE with high reproducibility.
Record Date Created: 20010815

21/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12718404 21564936 PMID: 11708614
AGES in brain ageing: AGE-inhibitors as neuroprotective and anti-dementia drugs?
Dukic-Stefanovic S; Schinzel R; Riederer P; Munch G
Physiological Chemistry I, Biocenter, University of Wurzburg, Germany.
Biogerontology (Netherlands) 2001, 2 (1) p19-34, ISSN 1389-5729 Journal Code: 100930043
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In Alzheimer's disease, age-related cellular changes such as compromised energy production and increased radical formation are worsened by the presence of AGEs as additional, AD specific stress factors. Intracellular AGEs (most likely derived from methylglyoxal) crosslink cytoskeletal proteins and render them insoluble. These aggregates inhibit cellular functions including transport processes and contribute to neuronal dysfunction and death. Extracellular AGEs, which accumulate in ageing tissue (but most prominently on long-lived protein deposits like the senile plaques) exert chronic oxidative stress on neurons. In addition, they activate glial cells to produce free radicals (superoxide and NO) and neurotoxic cytokines such as TNF-alpha. Drugs, which inhibit the formation of AGEs by specific chemical mechanisms (AGE-inhibitors), including aminoguanidine , carnosine, tenilsetam, OPB-9195 and pyridoxamine , attenuate the development of (AGE-mediated) diabetic complications. Assuming that ' carbonyl stress ' contributes significantly to the progression of Alzheimer's disease, AGE-inhibitors might also become interesting novel therapeutic drugs for treatment of AD. (84 Refs.)
Record Date Created: 20011115

21/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12534835 21408536 PMID: 11516257
The effect of aminoguanidine on diabetes-induced inactivation of kidney Na(+),K(+)- ATPase in rats.
Unlucerci Y; Kocak H; Seferoglu G; BekpInar S

Department of Biochemistry, Istanbul Faculty of Medicine, Istanbul University, Capa 34390-Istanbul, Turkey. yesimunlucerci@hotmail.com
Pharmacological research : the official journal of the Italian Pharmacological Society (England) Aug 2001, 44 (2) p95-8, ISSN 1043-6618 Journal Code: 8907422
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We studied the effect of aminoguanidine (AG), an inhibitor of advanced glycation product formation, on diabetes-induced oxidative damage. Renal cortex Na(+),K(+)- ATPase was chosen for study as a potential cellular target of oxygen radicals. In this study, the enzyme activity was reduced while malondialdehyde (MDA) and carbonyl levels were enhanced but sulphydryl (SH) level remained unchanged in the renal cortex in diabetic animals. Treatment of diabetic rats with AG had no significant effect on diabetes-induced impairments of enzyme activity and MDA but the carbonyl level readjusted to control level in the kidney. These results show that AG treatment at that dose did not exhibit profound antioxidant properties even if carbonyl stress was ameliorated by this treatment. Copyright 2001 Academic Press.
Record Date Created: 20010822

21/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11132837 21169733 PMID: 11270668
Advanced glycation end-products: a review.
Singh R; Barden A; Mori T; Beilin L
Dept of Medicine, University of Western Australia and West Australian Heart Researrch Institute, Perth, Australia.
Diabetologia (Germany) Feb 2001, 44 (2) p129-46, ISSN 0012-186X Journal Code: 0006777
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Advanced glycation end-products are a complex and heterogeneous group of compounds that have been implicated in diabetes related complications. At present it is not known if they are the cause or the consequence of the complications observed. We discuss the chemistry of advanced glycated end-product formation and their patho-biochemistry particularly in relation to the diabetic microvascular complications of retinopathy, neuropathy and nephropathy as well as their role in the accelerated vasculopathy observed in diabetes. The concept of carbonyl stress as a cause for advanced glycated end-product toxicity is mentioned. We discuss alterations in the concentrations of advanced glycated end-products in the body, particularly in relation to changes occuring with age, diabetes and its complications such as nephropathy. Problems relating to current methods of advanced glycated end-product detection and measurement are highlighted including the lack of a universally established method of detection or unit of measurement. Agents used for the treatment of advanced glycated end-product accumulation are reviewed, with an emphasis on the results of the recent phase III trials using aminoguanidine and diabetes related complications. (155 Refs.)
Record Date Created: 20010328

21/7/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11087420 21105616 PMID: 11168978
Reactive carbonyl compounds related uremic toxicity (" carbonyl stress").
Miyata T ; Sugiyama S; Saito A; Kurokawa K
Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Medicine, Tokai University School of Medicine, Isehara, Japan. t-miyata@is.icc.u-tokai.ac.jp
Kidney international. Supplement (United States) Feb 2001, 78 pS25-31 , ISSN 0098-6577 Journal Code: 7508622
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Many studies on uremic toxins have focused on enzymatic biochemistry. Recently, attention has turned to nonenzymatic biochemistry, especially progressive and irreversible modifications of proteins. Two different approaches opened the field of irreversible nonenzymatic modifications of proteins in uremia: the advanced glycation end products (AGEs) derived from the Maillard reaction and the advanced lipoxidation end products (ALEs) derived from lipid peroxidation. They have revealed the accumulation of reactive carbonyl compounds (RCOs) derived from carbohydrates and lipids and the subsequent carbonyl modifications of proteins (" carbonyl stress"). In this article, we describe the causal role of various RCOs and AGEs/ALEs accumulating in uremia, the clinical consequences of carbonyl stress in uremia, and finally, the therapeutic perspectives. We propose carbonyl stress as a new uremic toxicity. (66 Refs.)
Record Date Created: 20010222

21/7/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11065628 21067023 PMID: 11149912
Promoting glutathione synthesis after spinal cord trauma decreases secondary damage and promotes retention of function.
Kamencic H; Griebel R W; Lyon A W; Paterson P G; Juurlink B H
Department of Anatomy, University of Saskatchewan, Saskatoon, SK, Canada.
FASEB journal : official publication of the Federation of American Societies for Experimental Biology (United States) Jan 2001, 15 (1) p243-250, ISSN 0892-6638 Journal Code: 8804484
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The study aimed to 1) quantify oxidative stress in spinal cord after crush injury at T6, 2) determine whether the administration of the procysteine compound L-2-oxothiazolidine-4-carboxylate (OTC) would up-regulate glutathione (GSH) synthesis and decrease oxidative stress, and 3) determine whether decreased oxidative stress results in better tissue and function retention. We demonstrate that spinal cord compression (5 s with a 50 g aneurysm clip) at T6 in rats results in oxidative stress that is extensive (significant increases in oxidative stress seen at C3 and L4)

and rapid in onset. Indices of oxidative stress used were GSH content, protein carbonyl content, and inactivation of glutathione reductase. Administration of OTC resulted in a marked decrease in oxidative stress associated with a sparing of white matter at T6 (16+/-1.9% retained in OTC-treated animals vs. less than 1% in saline-treated). Behavioral indices in control, saline-treated, and OTC-treated animals after 6 wk were respectively: angle board scores (59 degrees, 32 degrees, and 42 degrees ), modified Tarlov score (7, 2.4, and 4.1), and Basso-Beattie-Bresnahan score (21, 5.3, and 12.9). We conclude that administration of OTC after spinal cord trauma greatly decreases oxidative stress and allows tissue preservation, thereby enabling otherwise paraplegic animals to locomote.

Record Date Created: 20010126

21/7/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10986444 20566764 PMID: 11115086

Effect of dwell time on carbonyl stress using icodextrin and amino acid peritoneal dialysis fluids.

Ueda Y; Miyata T ; Goffin E; Yoshino A; Inagi R; Ishibashi Y; Izuhara Y; Saito A; Kurokawa K; Van Ypersele De Strihou C

Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan.

Kidney international (UNITED STATES) Dec 2000, 58 (6) p2518-24, ISSN 0085-2538 Journal Code: 0323470

Document type: Clinical Trial; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Deterioration of the peritoneal membrane limits the technical survival of peritoneal dialysis (PD). Advanced glycation of the membrane has been incriminated in this evolution. Advanced glycation end products (AGEs) develop under the influence of glucose and of its degradation products, mainly reactive carbonyl compounds (RCOs) such as glyoxal (GO), methylglyoxal (MGO), and 3-deoxyglucosone (3-DG). The present study was undertaken to evaluate the impact of recently developed glucose-free PD fluids on AGE generation. METHODS: Recently developed glucose-free PD fluids containing either icodextrin or amino acids were investigated. GO, MGO, and 3-DG [high-performance liquid chromatography (HPLC)] and total RCOs (spectrophotometry) were measured in fresh solutions and in effluents after various dwell duration. The AGE formation potential of PD fluids and effluents was assessed by incubation at 37 degrees C, for one week, with bovine serum albumin and by the eventual measurement of pentosidine (HPLC) and Nepsilon-carboxymethyllysine (CML; gas chromatography/mass spectrometry). RESULTS: GO, MGO, and 3-DG ($P < 0.001$) as well as total RCOs levels ($P < 0.01$) were significantly lower in icodextrin and amino acid PD fluid than in commercial, heat-sterilized, 1.36% glucose PD fluid. Pentosidine and CML generation were also significantly lower ($P < 0.001$) in icodextrin and amino acid PD fluid than in conventional 1.36% glucose PD fluid. The levels of total RCOs, however, increased in icodextrin and amino acid PD fluid effluents with dwell time. AGE formation potential rose accordingly, as demonstrated by a parallel increase in the generation of pentosidine and CML during incubation of PD effluents. CONCLUSION: The present data demonstrate lower RCO contents and AGE formation potential in fresh icodextrin and amino acid PD fluids than

in fresh heat-sterilized glucose PD fluids. However, this difference decreases progressively during dwell time, mainly as a result of the influx of total RCOs.
Record Date Created: 20001221

21/7/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10877732 20422344 PMID: 10966497
Mechanism of the inhibitory effect of OPB-9195 [(+/-)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5-yla cetanilide] on advanced glycation end product and advanced lipoxidation end product formation.
Miyata T ; Ueda Y; Asahi K; Izuhara Y; Inagi R; Saito A; Van Ypersele De Strihou C; Kurokawa K
Molecular and Cellular Nephrology, Institute of Medical Sciences and Département of Internal Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan. t-miyata@is.icc.u-tokai.ac.jp
Journal of the American Society of Nephrology : JASN (UNITED STATES) Sep 2000, 11 (9) p1719-25, ISSN 1046-6673 Journal Code: 9013836
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The accumulation in uremic plasma of reactive carbonyl compounds (RCO) derived from both carbohydrates and lipids (" carbonyl stress ") contributes to uremic toxicity by accelerating the advanced glycation and lipoxidation of proteins. It was previously demonstrated that OPB-9195 [(+/-)-2-isopropylidenehydrazono-4-oxo- thiazolidin-5-ylacetanilide] inhibited the in vitro formation of advanced glycation end products (AGE) in uremic plasma. This study was designed to elucidate the mechanism of action of OPB-9195 by further delineating the AGE and advanced lipoxidation end product (ALE) precursors targeted by this drug. The inhibitory effects of OPB-9195 on the formation of two AGE (N:epsilon-carboxymethyllysine and pentosidine) on bovine serum albumin incubated with various AGE precursors were examined. Inhibition of N:epsilon-carboxymethyllysine and pentosidine formation with OPB-9195 was more efficient than with aminoguanidine . OPB-9195 also proved effective in blocking the carbonyl amine chemical processes involved in the formation of two ALE (malondialdehyde-lysine and 4-hydroxynonenal-protein adduct). The efficiency of OPB-9195 was similar to that of aminoguanidine . When glucose-based peritoneal dialysis fluid was incubated in the presence of OPB-9195, a similar inhibition of AGE formation was observed. The direct effect of OPB-9195 on major glucose-derived RCO in peritoneal dialysis fluids was then evaluated. The effects of OPB-9195 could be accounted for by its ability to trap RCO. The concentrations of three major glucose-derived RCO (glyoxal, methylglyoxal, and 3-deoxy-glucosone) were significantly lower in the presence of OPB-9195 than in its absence. Aminoguanidine had a similar effect. In conclusion, OPB-9195 inhibits both AGE and ALE formation, probably through its ability to trap RCO. OPB-9195 might prove to be a useful tool to inhibit some of the effects of RCO-related uremic toxicity.
Record Date Created: 20000918

21/7/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10787816 20345574 PMID: 10886591

Advanced glycation and lipidoxidation of the peritoneal membrane: respective roles of serum and peritoneal fluid reactive carbonyl compounds.

Miyata T ; Horie K; Ueda Y; Fujita Y; Izuhara Y; Hirano H; Uchida K; Saito A; van Ypersele de Strihou C; Kurokawa K

Molecular and Cellular Nephrology, Institute of Medical Sciences, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan.

Kidney international (UNITED STATES) Jul 2000, 58 (1) p425-35, ISSN 0085-2538 Journal Code: 0323470

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Advanced glycation of proteins has been incriminated in the progressive alteration of the peritoneal membrane during chronic peritoneal dialysis (PD). Advanced glycation end products (AGEs) result from a modification of proteins by reactive carbonyl compounds (RCOs). RCOs resulting from glucose breakdown are present in commercial PD fluid. They also accumulate in uremic plasma. The present study was undertaken to evaluate the respective contribution of these two sources of RCOs in the genesis of peritoneal AGEs. METHODS: Three major RCOs formed during heat sterilization of PD fluid, that is, glyoxal, methylglyoxal, and 3-deoxyglucosone, and total RCOs were measured in commercial PD fluid and in PD effluent. The generation of pentosidine, used as a surrogate marker for AGEs, during one-week incubations of PD fluid and effluent samples fortified with bovine serum albumin (BSA) was measured by high-performance liquid chromatography. Peritoneal samples were stained with antibodies specific for two AGEs derived from carbohydrate-dependent RCOs, Nepsilon-(carboxymethyl)lysine (CML) and pentosidine, or for two advanced lipoxidation end products (ALEs) derived from lipid-dependent RCOs, malondialdehyde (MDA)-lysine and 4-hydroxynonenal (HNE)-protein adduct. RESULTS: Glyoxal, methylglyoxal, and 3-deoxyglucosone were identified in commercial PD fluid. Their levels in PD effluents decreased with dwell time probably by diffusion into blood circulation. In contrast, the levels of total RCOs were initially low in commercial PD fluid, increased in PD effluent with dwell time probably by diffusion from circulation into the peritoneal cavity, and after 12 hours, reached values observed in uremic serum. The relevance of the rise in total RCOs for AGE formation is demonstrated by a parallel increase in the generation of pentosidine during incubations of PD effluents. In contrast with RCOs present in glucose-rich PD fluid, RCOs diffusing from uremic circulation originate from both carbohydrates and lipids. Their role in the modification of peritoneal proteins is demonstrated by the immunohistochemical study of peritoneal tissue. Two AGEs and two ALEs increase in parallel in the mesothelial layers and in vascular wall of small arteries in the peritoneum. CONCLUSIONS: Protein modification of the peritoneum is determined not only by RCOs originating in PD fluid, but also by RCOs originating from the uremic circulation. The present data might be relevant to current attempts to improve PD fluid toxicity by lowering its glucose content.

Record Date Created: 20000821

10624371 20160409 PMID: 10692262
Advanced glycation end products: a Nephrologist's perspective.
Raj D S; Choudhury D; Welbourne T C; Levi M
Department of Medicine, Lousiana State University Medical Center, Shreveport, LA,USA.
American journal of kidney diseases : the official journal of the National Kidney Foundation (UNITED STATES) Mar 2000, 35 (3) p365-80, ISSN 1523-6838 Journal Code: 8110075
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Advanced glycation end products (AGEs) are a heterogeneous group of molecules that accumulate in plasma and tissues with advancing age, diabetes, and renal failure. There is emerging evidence that AGEs are potential uremic toxins and may have a role in the pathogenesis of vascular and renal complications associated with diabetes and aging. AGEs are formed when a carbonyl of a reducing sugar condenses with a reactive amino group in target protein. These toxic molecules interact with specific receptors and elicit pleiotropic responses. AGEs accelerate atherosclerosis through cross-linking of proteins, modification of matrix components, platelet aggregation, defective vascular relaxation, and abnormal lipoprotein metabolism. In vivo and in vitro studies indicate that AGEs have a vital role in the pathogenesis of diabetic nephropathy and the progression of renal failure. The complications of normal aging, such as loss of renal function, Alzheimer's disease, skin changes, and cataracts, may also be mediated by progressive glycation of long-lived proteins. AGEs accumulate in renal failure as a result of decreased excretion and increased generation resulting from oxidative and carbonyl stress of uremia. AGE-modified beta(2)-microglobulin is the principal pathogenic component of dialysis-related amyloidosis in patients undergoing dialysis. Available dialytic modalities are not capable of normalizing AGE levels in patients with end-stage renal disease. A number of reports indicated that restoration of euglycemia with islet-cell transplantation normalized and prevented further glycosylation of proteins. Aminoguanidine (AGN), a nucleophilic compound, not only decreases the formation of AGEs but also inhibits their action. A number of studies have shown that treatment with AGN improves neuropathy and delays the onset of retinopathy and nephropathy. N-Phenacylthiazolium bromide is a prototype AGE cross-link breaker that reacts with and can cleave covalent AGE-derived protein cross-links. Thus, there is an exciting possibility that the complications of diabetes, uremia, and aging may be prevented with these novel agents. ( 146 Refs.)

Record Date Created: 20000314

21/7/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10513683 20036029 PMID: 10571251
Reaction of metformin with dicarbonyl compounds. Possible implication in the inhibition of advanced glycation end product formation.
Ruggiero-Lopez D; Lecomte M; Moinet G; Patereau G; Lagarde M; Wiernsperger N
Diabetic Microangiopathy Research Unit, LIPHA-INSERM U352, INSA-Lyon, Villeurbanne, France. ruggiero@insa.insa-lyon.fr

Biochemical pharmacology (ENGLAND) Dec 1 1999, 58 (11) p1765-73,
ISSN 0006-2952 Journal Code: 0101032
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Dicarbonyl compounds such as methylglyoxal and glyoxal are extremely reactive glycating agents involved in the formation of advanced glycation end products (AGEs), which in turn are associated with diabetic vascular complications. Guanidino compounds such as aminoguanidine appear to inhibit AGE formation by reacting with alpha-dicarbonyl compounds. The aim of this work was to study whether the antihyperglycemic agent metformin (a guanidine-like compound) might react with reactive alpha-dicarbonyls. Metformin was incubated at pH 7.4 and 37 degrees in the presence of either methylglyoxal or glyoxal and reaction products analysed by HPLC coupled to mass tandem spectrometry. AGE formation on albumin by methylglyoxal and glyoxal in the presence or absence of metformin was also studied by measuring the fluorescence at 370/440 nm after albumin-AGE isolation by ultrafiltration. As a standard for mass spectra analysis, a metformin-methylglyoxal adduct was chemically synthesised and characterised as a triazepinone (2-amino-4-(dimethyl-amino)-7-methyl-5,7-dihydro-6H-[1,3,5]triazepin+ ++-6-one). The results obtained showed that metformin strongly reacted with methylglyoxal and glyoxal, forming original guanidine-dicarbonyl adducts. Reaction kinetic studies as well as mass fragmentation spectra of the reaction products were compatible with the presence of triazepinone derivatives. In the presence of metformin, AGE-related fluorescence after albumin incubation with either glyoxal or methylglyoxal was decreased by 37% and 45%, respectively. These results suggest that besides its known antihyperglycemic effect, metformin could also decrease AGE formation by reacting with alpha-dicarbonyl compounds. This is relevant to a potential clinical use of metformin in the prevention of diabetic complications by inhibition of carbonyl stress .

Record Date Created: 19991217

21/7/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10370732 99362631 PMID: 10432417

Critical evaluation of plasma and LDL oxidant-trapping potential in hemodialysis patients.

Nguyen-Khoa T; Massy Z A; Witko-Sarsat V; Thevenin M; Touam M; Lambrey G; Lacour B; Drueke T B; Descamps-Latscha B
INSERM U507, Division of Nephrology, Necker Hospital, Paris, France.

Kidney international (UNITED STATES) Aug 1999, 56 (2) p747-53,
ISSN 0085-2538 Journal Code: 0323470
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

BACKGROUND: We investigated whether the total peroxyl radical-trapping antioxidant potential (TRAP) assay, which has recently been proposed as a gauge of oxidative stress, could serve to evaluate plasma and low density lipoprotein (LDL) antioxidant state in hemodialysis (HD) patients. METHODS: TRAP was determined by the lag time of the chemiluminescence reaction induced by azo-initiator-catalyzed linoleic acid peroxidation in the plasma and corresponding LDL preparations of 23 HD patients and 22 healthy

subjects. Antioxidant systems, including glutathione peroxidase (GSH-Px), ascorbate, vitamin E, and uric acid, oxidative stress markers including malondialdehyde (MDA), carbonyls , and advanced oxidation protein products (AOPP), and lipids, including cholesterol and triglycerides, were also determined in the plasma. RESULTS: Both plasma and LDL-TRAP were significantly increased in HD patients despite decreased GSH-Px and ascorbate and increased MDA, carbonyl , and AOPP plasma levels. Plasma TRAP values were closely related to both uric acid and AOPP levels, and LDL-TRAP values were related to triglycerides and AOPP levels. In vitro studies showed that: (a) plasma TRAP of control plasma increased regularly with supplementation of uric acid, although not reaching that of HD plasma with similar uric acid levels; (b) the addition of human serum albumin-AOPP also regularly increased control plasma TRAP, but was close to that of HD plasma with similar AOPP levels; and (c) LDL-TRAP was increased following LDL enrichment with triglycerides. CONCLUSION: Our study demonstrates that TRAP is not a relevant parameter for evaluating plasma or LDL antioxidant capacity in HD patients, due to the high plasma levels of uric acid, triglycerides and AOPP, which by themselves do not exert efficient antioxidant activity in vivo, but in vitro are able to scavenge the peroxyl radicals involved in the TRAP assay.

Record Date Created: 19990830

21/7/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10345833 99333153 PMID: 10406495

Carbonyl stress: increased carbonyl modification of tissue and cellular proteins in uremia.

Miyata T ; Izuhara Y; Sakai H; Kurokawa K

Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan.

Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis (CANADA) 1999, 19 Suppl 2 pS58-61, ISSN 0896-8608 Journal Code: 8904033

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Advanced glycation end-products (AGEs) are formed during non enzymatic glycation and oxidation (glycoxidation) reactions.This process is accelerated in diabetics owing to hyperglycemia, and it has been implicated in the pathogenesis of diabetic complications. Surprisingly, AGEs increase in normoglycemic uremic patients to a much greater extent than in diabetics. AGE accumulation in uremia cannot be attributed to hyperglycemia nor simply to a decreased removal by glomerular filtration. Recently gathered evidence has suggested that, in uremia, the increased carbonyl compounds derived from carbohydrates and lipids modify proteins not only by glycoxidation reaction but also by lipoxidation reaction (" carbonyl stress"). Carbonyl stress has been implicated in the pathogenesis of long-term uremic complications such as dialysis-related amyloidosis. With regard to continuous ambulatory peritoneal dialysis (CAPD), the peritoneal cavity appears to be in a state of severe overload of carbonyl compounds derived from CAPD solution containing high glucose, from heat sterilization of the solution, and from uremic circulation. Carbonyl stress might modify not only peritoneal matrix proteins and alter their structures, but also react with mesothelial and endothelial

cell surface proteins and initiate a range of inflammatory responses. Carbonyl stress might therefore contribute to the development of peritoneal sclerosis in patients with long-term CAPD.
Record Date Created: 19990824

21/7/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10345807 99333214 PMID: 10406556
Beta2-microglobulin and renal bone disease.
Wada T; Miyata T ; Sakai H; Kurokawa K
Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan.
Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis (CANADA) 1999, 19 Suppl 2 pS413-6, ISSN 0896-8608 Journal Code: 8904033
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Dialysis-related amyloidosis (DRA) is characterized by amyloid deposition mainly in bone and joint structures, presenting as carpal tunnel syndrome, destructive arthropathy, and subchondral bone erosions and cysts. Beta2-microglobulin has been demonstrated to be a major constituent of amyloid fibrils. DRA occurs not only in patients undergoing long-term hemodialysis, but also in patients undergoing continuous ambulatory peritoneal dialysis . The incidence of this complication increases with the duration of dialytic therapy and the age of the patient. While a definitive diagnosis of DRA can be made only by histological findings, various imaging techniques often support diagnosis. The molecular pathogenesis of this complication remains unknown. Recent studies have, however, suggested a pathogenic role of a new modification of beta2-microglobulin in amyloid fibrils--that is, the advanced glycation end-products (AGEs) formed with carbonyl compounds derived from autoxidation of both carbohydrates and lipids (" carbonyl stress"). Therapy for DRA is limited to symptomatic approaches and surgical removal of amyloid deposits. High-flux biocompatible dialysis membranes could be used to delay DRA development. (21 Refs.)
Record Date Created: 19990824

21/7/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10229568 99208145 PMID: 10193802
A sensitive and specific ELISA for plasma pentosidine.
Izuhara Y; Miyata T ; Ueda Y; Suzuki D; Asahi K; Inagi R; Sakai H; Kurokawa K
Molecular and Cellular Nephrology, Institute of Medical Sciences and Department of Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan.
Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association ( ENGLAND) Mar 1999, 14 (3) p576-80, ISSN 0931-0509 Journal Code: 8706402
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

BACKGROUND: Advanced glycation end products are formed by non-enzymatic glycation and oxidation reaction. Pentosidine is a well-known and characterized structure among them, and has been implicated in the pathogenesis of complications associated with chronic renal failure and long-term dialysis, such as dialysis-related amyloidosis and atherosclerosis. METHODS: We established a highly sensitive and specific competitive enzyme-linked immunosorbent assay (ELISA) for plasma pentosidine and applied it to large numbers of plasma samples including haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients. We compared their plasma pentosidine levels determined by the competitive ELISA with those determined by high-performance liquid chromatographic (HPLC) assay currently used. RESULTS: The plasma pentosidine levels determined by the ELISA were correlated well with those determined by sophisticated instrumental HPLC assay, both in non-diabetic and diabetic dialysis patients. Both analyses yielded comparable results, with over 8-fold higher plasma pentosidine levels in HD and CAPD patients, irrespective of the presence or absence of diabetes, as compared to normal subjects and non-uraemic diabetic patients. CONCLUSIONS: The competitive ELISA will provide a rapid and convenient determination of plasma pentosidine content and thus be useful to assess the carbonyl stress in uraemic patients.

Record Date Created: 19990527

21/7/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10170136 99141537 PMID: 9987064

Alterations in nonenzymatic biochemistry in uremia: origin and significance of " carbonyl stress " in long-term uremic complications.

Miyata T; van Ypersele de Strihou C; Kurokawa K; Baynes J W

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Kidney international (UNITED STATES) Feb 1999, 55 (2) p389-99, ISSN 0085-2538 Journal Code: 0323470

Contract/Grant No.: AG-11472; AG; NIA; DK-19971; DK; NIDDK

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Advanced glycation end products (AGEs), formed during Maillard or browning reactions by nonenzymatic glycation and oxidation (glycoxidation) of proteins, have been implicated in the pathogenesis of several diseases, including diabetes and uremia. AGEs, such as pentosidine and carboxymethyllysine, are markedly elevated in both plasma proteins and skin collagen of uremic patients, irrespective of the presence of diabetes. The increased chemical modification of proteins is not limited to AGEs, because increased levels of advanced lipoxidation end products (ALEs), such as malondialdehydelysine, are also detected in plasma proteins in uremia. The accumulation of AGEs and ALEs in uremic plasma proteins is not correlated with increased blood glucose or triglycerides, nor is it determined by a decreased removal of chemically modified proteins by glomerular filtration. It more likely results from increased plasma concentrations of small, reactive carbonyl precursors of AGEs and ALEs, such as glyoxal,

methylglyoxal, 3-deoxyglucosone, dehydroascorbate, and malondialdehyde. Thus, uremia may be described as a state of carbonyl overload or " carbonyl stress " resulting from either increased oxidation of carbohydrates and lipids (oxidative stress) or inadequate detoxification or inactivation of reactive carbonyl compounds derived from both carbohydrates and lipids by oxidative and nonoxidative chemistry. Carbonyl stress in uremia may contribute to the long-term complications associated with chronic renal failure and dialysis, such as dialysis-related amyloidosis and accelerated atherosclerosis. The increased levels of AGEs and ALEs in uremic blood and tissue proteins suggest a broad derangement in the nonenzymatic biochemistry of both carbohydrates and lipids. (90 Refs.)

Record Date Created: 19990415

21/7/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10089884 99063536 PMID: 9848790

Accumulation of carbonyls accelerates the formation of pentosidine, an advanced glycation end product: carbonyl stress in uremia.

Miyata T; Ueda Y; Yamada Y; Izuhara Y; Wada T; Jadoul M; Saito A; Kurokawa K; van Ypersele de Strihou C

Institute of Medical Sciences and Department of Medicine, Tokai University School of Medicine, Isehara, Japan.

Journal of the American Society of Nephrology : JASN (UNITED STATES) Dec 1998, 9 (12) p2349-56, ISSN 1046-6673 Journal Code: 9013836

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Advanced glycation end product (AGE) formation is related to hyperglycemia in diabetes but not in uremia, because plasma AGE levels do not differ between diabetic and nondiabetic hemodialysis patients. The mechanism of this phenomenon remains elusive. Previously, it was suggested that elevation of AGE levels in uremia might result from the accumulation of unknown AGE precursors. The present study evaluates the in vitro generation of pentosidine, a well identified AGE structure. Plasma samples from healthy subjects and nondiabetic hemodialysis patients were incubated under air for several weeks. Pentosidine levels were determined at intervals by HPLC assay. Pentosidine rose to a much larger extent in uremic than in control plasma. Pentosidine yield, i.e., the change in pentosidine level between 0 and 4 wk divided by 28 d, averaged 0.172 nmol/ml per d in uremic versus 0.072 nmol/ml per d in control plasma ($P < 0.01$). The difference in pentosidine yield between uremic and control plasma was maintained in samples ultrafiltrated through a filter with a 5000-Da cutoff value and fortified with human serum albumin (0.099 versus 0.064 nmol/ml per d; $P < 0.05$). Pentosidine yield was higher in pre- than in postdialysis plasma samples (0.223 versus 0.153 nmol/ml per d; $P < 0.05$). These results suggest that a large fraction of the pentosidine precursors accumulated in uremic plasma have a lower than 5000 Da molecular weight. Addition of aminoguanidine and OPB-9195, which inhibit the Maillard reaction, lowered pentosidine yield in both uremic and control plasma. When ultrafiltrated plasma was exposed to 2,4-dinitrophenylhydrazine, the yield of hydrazones, formed by interaction with carbonyl groups, was markedly higher in uremic than in control plasma. These observations strongly suggest that the pentosidine precursors accumulated in uremic plasma are carbonyl compounds.

These precursors are unrelated to glucose or ascorbic acid, whose concentration is either normal or lowered in uremic plasma. They are also unrelated to 3-deoxyglucosone, a glucose-derived dicarbonyl compound whose level is raised in uremic plasma: Its addition to normal plasma fails to increase pentosidine yield. This study reports an elevated level of reactive carbonyl compounds (" carbonyl stress ") in uremic plasma. Most have a lower than 5000 Da molecular weight and are thus partly removed by hemodialysis. Their effect on pentosidine generation can be inhibited by aminoguanidine or OPB-9195. Carbonyl stress might contribute to AGE modification of proteins and thus to clinically relevant complications of uremia.

Record Date Created: 19990419

21/7/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07831973 93361501 PMID: 8395050

Tat protein of human immunodeficiency virus type 1 represses expression of manganese superoxide dismutase in HeLa cells.

Flores S C; Marecki J C; Harper K P; Bose S K; Nelson S K; McCord J M

Webb-Waring Institute for Biomedical Research, University of Colorado Health Sciences Center, Denver 80262.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Aug 15 1993, 90 (16) p7632-6, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: 5P50 HL40784-SCOR-MIRS; HL; NHLBI; T32 DK07658; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Using a HeLa cell line stably transfected with the tat gene from human immunodeficiency virus type 1, we have found that the expression of the regulatory Tat protein suppresses the expression of cellular Mn-containing superoxide dismutase (Mn-SOD). This enzyme is one of the cell's primary defenses against oxygen-derived free radicals and is vital for maintaining a healthy balance between oxidants and antioxidants. The parental HeLa cells expressed nearly equivalent amounts of Cu,Zn- and Mn-SOD isozymes. Those cells expressing the Tat protein, however, contained 52% less Mn-SOD activity than parental cells, whereas that of the Cu,Zn enzyme was essentially unchanged. The steady-state levels of Mn-SOD-specific RNAs were also lower in the HeLa-tat cell line than in the parental line. No difference was seen in the steady-state levels of Cu,Zn-SOD-specific RNAs. In addition to the decreased Mn-SOD-activity, HeLa-tat cell showed evidence of increased oxidative stress . Carbonyl proteins were markedly higher, and total cellular sulfhydryl content decreased in cell extracts at a faster rate, probably reflecting ongoing lipid peroxidation. HeLa and HeLa-tat extracts were incubated with radiolabeled Mn-SOD transcripts, and the reaction products were subjected to UV crosslinking, digestion with ribonuclease A, and electrophoretic analysis. The results suggest a direct interaction between Tat protein and Mn-SOD gene transcripts.

Record Date Created: 19930923

21/7/24 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13671338 BIOSIS NO.: 200200300159
Efficient lowering of carbonyl stress by the glyoxalase system in peritoneal dialysis .
AUTHOR: Inagi Reiko(a); Miyata Toshio (a); Ueda Yasuhiko(a); Nangaku Masaomi; de Strihou Charles van Ypersele; Kurokawa Kiyoshi(a
AUTHOR ADDRESS: (a)Inst of Med Sci and Dept of Med, Tokai Univ Sch of Med, Kanagawa**Japan
JOURNAL: Journal of the American Society of Nephrology 12 (Program and Abstract Issue):p429A September, 2001
MEDIUM: print
CONFERENCE/MEETING: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/25 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


13613727 BIOSIS NO.: 200200242548
Decrease of glucose degradation reactive carbonyl compounds ( Carbonyl stress) by glyoxalase and glutathione in peritoneal dialysis (PD) fluid.
AUTHOR: Ueda Yasuhiko(a); Miyata Toshio (a); Izuhara Yuko(a); Inagi Reiko (a); Saito Akira(a); Sakai Hideto(a); Kurokawa Kiyoshi(a
AUTHOR ADDRESS: (a)Inst of Med Sci and Dept of Int Med, Tokai Univ Sch of Med, Isehara, Kanagawa**Japan
JOURNAL: Journal of the American Society of Nephrology 11 (Program and Abstract Issue):p220A September, 2000
MEDIUM: print
CONFERENCE/MEETING: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario, Canada October 10-16, 2000
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/26 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


13595954 BIOSIS NO.: 200200224775
Does removal of glucose lower the carbonyl stress of glucose containing peritoneal dialysate ? Effect of dwell time on icodextrin and amino acid PD fluids.
AUTHOR: Izuhara Yuko(a); Miyata Toshio (a); Ueda Yasuhiko(a); Goffin Eric; Inagi Reiko(a); Saito Akira(a); Kurokawa Kiyoshi(a); van Ypersele de Strihou Charles
AUTHOR ADDRESS: (a)Inst of Med Sci and Dept Int Med, Tokai Univ Sch of Med, Isehara, Kanagawa**Japan
JOURNAL: Journal of the American Society of Nephrology 11 (Program and

Abstract Issue):p210A September, 2000
MEDIUM: print
CONFERENCE/MEETING: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario, Canada October 10-16, 2000
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/27 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


13288497 BIOSIS NO.: 200100495646
Reactive carbonyl compounds as uremic toxins.
BOOK TITLE: Contributions to Nephrology Dialysis, dialyzers and sorbents: Where are we going?
AUTHOR: Miyata Toshio (a); Akhand Anwarul A; Kurokawa Kiyoshi; Nakashima Izumi
BOOK AUTHOR/EDITOR: Ronco C; Winchester J F: Eds
AUTHOR ADDRESS: (a)Molecular and Cellular Nephrology Institute of Medical Sciences and Department of Internal Medicine, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, 259-1143: t-miyata@is.icc.u-tokai.ac.jp**Japan
JOURNAL: Contributions to Nephrology 133p71-80 2001
MEDIUM: print
BOOK PUBLISHER: S. Karger AG, CH-4009, Basel, Switzerland
ISSN: 0302-5144 ISBN: 3-8055-7225-5 (cloth)
DOCUMENT TYPE: Book
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

21/7/28 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


12238208 BIOSIS NO.: 199900533057
2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide (OPB-9195) inhibits the glycoxidation reaction in glucose based peritoneal dialysis fluid.
AUTHOR: Ueda Yasuhiko(a); Miyata Toshio (a); Asahi Koichi(a); Izuhara Yuko (a); Inagi Reiko(a); Nangaku Masaomi(a); Ishibashi Yoshitaka(a); Sakai Hideto(a); Saito Akira(a); Kurokawa Kiyoshi(a
AUTHOR ADDRESS: (a)Inst. Med. Sci. and Dept. Int. Med., Tokai Univ. Sch. Med., Isehara, Kanagawa**Japan
JOURNAL: Journal of the American Society of Nephrology 10 (PROGRAM AND ABSTR. ISSUE):p324A Sept., 1999
CONFERENCE/MEETING: 32nd Annual Meeting of the American Society of Nephrology Miami Beach, Florida, USA November 1-8, 1999
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/29 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


12238186 BIOSIS NO.: 199900533035
Immunohistochemical detection of carbonyl stress, vascular endothelial growth factor (VEGF), and endothelial nitric oxide synthase (eNOS) in peritoneal tissues of peritoneal dialysis patients.
AUTHOR: Horie Katsunori(a); Miyata Toshio ; Devuyst Olivie; Inagi Reiko; Nangaku Masaomi; Sakai Hideto; Saito Akira; Maeda Kenji(a); Kurokawa Kiyoshi
AUTHOR ADDRESS: (a)Daiko Med. Ctr., Nagoya Univ. Sch. Med., Nagoya**Japan
JOURNAL: Journal of the American Society of Nephrology 10 (PROGRAM AND ABSTR. ISSUE):p315A Sept., 1999
CONFERENCE/MEETING: 32nd Annual Meeting of the American Society of Nephrology Miami Beach, Florida, USA November 1-8, 1999
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/30 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


12233016 BIOSIS NO.: 199900527865
Glucose-derived carbonyl compounds in PD fluids cross-links mesothelial cell surface protein for stimulating vascular endothelial growth factor (VEGF) and mitogen-activated protein kinases (MAPK).
AUTHOR: Inagi Reiko(a); Miyata Toshio (a); Ahkand Anwarul A; Sakai Hideto (a); Saito Akira(a); Nakashima Izumi; Kurokawa Kiyoshi(a
AUTHOR ADDRESS: (a)Inst. Med. Sci. and Dept. Int. Med., Tokai Univ. Sch. Med., Bohseidai, Kanagawa**Japan
JOURNAL: Journal of the American Society of Nephrology 10 (PROGRAM AND ABSTR. ISSUE):p315A Sept., 1999
CONFERENCE/MEETING: 32nd Annual Meeting of the American Society of Nephrology Miami Beach, Florida, USA November 1-8, 1999
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/31 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


12222270 BIOSIS NO.: 199900517119
Lower carbonyl stress in polyglucose or amino acid PD solutions than in conventional glucose based PD fluids.
AUTHOR: Ueda Yasuhiko(a); Miyata Toshio (a); Izuhara Yuko(a); Inagi Reiko (a); Nangaku Masaomi(a); Ishibashi Yoshitaka(a); Sakai Hideto(a); Saito Akira(a); Kurokawa Kiyoshi(a
AUTHOR ADDRESS: (a)Dept. Int. Med., Inst. Med. Sci., Tokai Univ. Sch. Med., Isehara, Kanagawa**Japan

JOURNAL: Journal of the American Society of Nephrology 10 (PROGRAM AND ABSTR. ISSUE):p230A Sept., 1999
CONFERENCE/MEETING: 32nd Annual Meeting of the American Society of Nephrology Miami Beach, Florida, USA November 1-8, 1999
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/32 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)


11766327 BIOSIS NO.: 199900012436
Immunohistochemical evidence for an increased carbonyl modification of peritoneal tissues by autoxidation products of carbohydrates and lipids in continuous ambulatory peritoneal dialysis (CAPD) patients.
AUTHOR: Horie Katsunori(a); Miyata Toshio ; Hirano Hiroshi; Yasuda Yoshinari; Devuyst Oliver; Saito Akira; Kurokawa Kiyoshi; Maeda Kenji
AUTHOR ADDRESS: (a)Nagoya Univ. Sch. Med., Nagoya**Japan
JOURNAL: Journal of the American Society of Nephrology 9 (PROGRAM AND ABSTR. ISSUE):p284A Sept., 1998
CONFERENCE/MEETING: 31st Annual Meeting of the American Society of Nephrology Philadelphia, Pennsylvania, USA October 25-28, 1998
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
RECORD TYPE: Citation
LANGUAGE: English

21/7/33 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE


11595221 EMBASE No: 2002166783
Effects of aminoguanidine on lipid and protein oxidation in diabetic rat kidneys
Gogas Yavuz D.; Kuc(cedil)ukkaya B.; Onder Ersoz H.; Suha Yalc(cedil)in A.; Emerk K.; Akalin S.
D. Gogas Yavuz, Dept. of Internal Medicine, Section of Endocrinology/Metabolism, Marma University, Moda Cad. Sakizgulu Sok. No:1-3/15, 81030 Istanbul Turkey
AUTHOR EMAIL: dyavuz@turk.net
International Journal of Experimental Diabetes Research ( INT. J. EXP. DIABETES RES. ) (United Kingdom) 2002, 3/2 (145-151)
CODEN: IEDRF ISSN: 1560-4284
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 28

Nonenzymatic glycation of tissue and plasma proteins may stimulate the production of oxidant and carbonyl stress in diabetes. The aim of this study was to evaluate the effects of aminoguanidine (AG) on lipid peroxidation, protein oxidation and nitric oxide (NO) release in diabetic rat kidneys. After induction of diabetes with streptozotocin, female Wistar rats were divided into 2 groups. Group DAG (n=9) rats were given AG

hydrogen carbonate (1 g/L) in drinking water and group D (n=8) was diabetic control rats given only tap water. Group H (n=8) was followed as healthy controls. At the end of an 8 week period, NO release, lipid and protein oxidation were determined in kidney tissues. NO release was significantly lower in diabetic rats compared with healthy controls ($p<0.05$). Lipid peroxidation was significantly high in group D (3.9 +/- 0.3 nmol MDA/g tissue) compared with the group DAG (2.6 +/- 0.1 nmol MDA/g tissue, $p<0.01$) and group H (2.4 +/- 0.2 nmol MDA/g tissue). Protein oxidation was significantly higher in diabetics than healthy controls (563.8 +/- 23.9, 655.8 +/- 7.2, 431.5 +/- 8.8 mmol carbonyl/g tissue for group DAG, D and H, respectively, $p< 0.05$). A positive correlation between albuminuria and thiobarbituric acid reactive substance (TBARS) levels ($r= 0.54, p<0.005$) and carbonyl content ($r=0.70$, $p<0.0005$) in kidney homogenate were observed. Although AG treatment had no effect on NO release, it significantly decreased lipid peroxidation in diabetic rat cortices. Consequently increased lipid peroxidation -as well as- protein oxidation could be involved in the pathogenesis of diabetic albuminuria.

21/7/34 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE


11574320 EMBASE No: 2002144817
Molecular mechanisms of peritoneal permeability - Research growth factors
Devuyst O.
O. Devuyst, Division of Nephrology, UCL Medical School, 10 Avenue Hippocrate, Brussels B-1200 Belgium
AUTHOR EMAIL: devuyst@nefr.ucl.ac.be
Peritoneal Dialysis International ( PERITONEAL DIAL. INT. ) (Canada) 2001, 21/SUPPL. 3 (S19-S23)
CODEN: PDIIE ISSN: 0896-8608
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 37

21/7/35 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE


11565569 EMBASE No: 2002136827
Inhibition of Rho GTPases with protein prenyltransferase inhibitors prevents leukocyte recruitment to the central nervous system and attenuates clinical signs of disease in an animal model of multiple sclerosis
Walters C.E.; Pryce G.; Hankey D.J.R.; Sebti S.M.; Hamilton A.D.; Baker D.; Greenwood J.; Adamson P.
Dr. P. Adamson, Department of Cell Biology, Institute of Ophthalmology, Bath Street, London EC1V 9EL United Kingdom
AUTHOR EMAIL: padamson@hgmp.mrc.ac.uk
Journal of Immunology ( J. IMMUNOL. ) (United States) 15 APR 2002, 168/8 (4087-4094)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 41

The ICAM-1-mediated brain endothelial cell (EC)-signaling pathway induced by adherent lymphocytes is a central element in facilitating lymphocyte migration through the tight endothelial barrier of the brain. Rho proteins, which must undergo post-translational prenylation to be functionally active, have been shown to be an essential component of this signaling cascade. In this study, we have evaluated the effect of inhibiting protein prenylation in brain ECs on their ability to support T lymphocyte migration. ECs treated in vitro with protein prenylation inhibitors resulted in a significant reduction in transendothelial T lymphocyte migration. To determine the therapeutic potential of this approach, an animal model of multiple sclerosis, experimental autoimmune encephalomyelitis, was induced in Biozzi ABH mice. Animals treated before disease onset with protein prenylation inhibitors exhibited a dramatic and significant reduction in both leukocyte infiltration into the CNS and clinical presentation of disease compared with untreated animals. These studies demonstrate, for the first time, the potential for pharmacologically targeting CNS EC signaling responses, and particularly endothelial Rho proteins, as a means of attenuating leukocyte recruitment to the CNS.

21/7/36 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE


11252209 EMBASE No: 2001267136
The effect of aminoguanidine on diabetes-induced inactivation of kidney NaSUP+,KSUP+- atpase in rats
Unluc(cedil)erc(cedil)i Y.; Koc(cedil)ak H.; Seferog(caron)lu G.; Bekpinar S.
Y. Unluc(cedil)erc(cedil)i, Department of Biochemistry, Istanbul Faculty of Medicine, Istanbul University, C(cedil)apa 34390-Istanbul Turkey
AUTHOR EMAIL: yesimunlucerci@hotmail.com
Pharmacological Research ( PHARMACOL. RES. ) (United Kingdom) 2001, 44/2 (95-98)
CODEN: PHMRE ISSN: 1043-6618
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 18

We studied the effect of aminoguanidine (AG), an inhibitor of advanced glycation product formation, on diabetes-induced oxidative damage. Renal cortex NaSUP+,KSUP+-ATPase was chosen for study as a potential cellular target of oxygen radicals. In this study, the enzyme activity was reduced while malondialdehyde (MDA) and carbonyl levels were enhanced but sulphydryl (SH) level remained unchanged in the renal cortex in diabetic animals. Treatment of diabetic rats with AG had no significant effect on diabetes-induced impairments of enzyme activity and MDA but the carbonyl level readjusted to control level in the kidney. These results show that AG treatment at that dose did not exhibit profound antioxidant properties even if carbonyl stress was ameliorated by this treatment. (c) 2001 Academic Press.

21/7/37 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

11251051 EMBASE No: 2001265777

1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylamino)carbonylhydrazine (101M): A novel sulfonylhydrazine prodrug with bbroad-spectrum antineoplastic activity

Finch R.A.; Shyam K.; Penketh P.G.; Sartorelli A.C.
A.C. Sartorelli, Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520 United States
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Cancer Research ( CANCER RES. ) (United States) 01 APR 2001, 61/7 (3033-3038)
CODEN: CNREA ISSN: 0008-5472
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35

Our laboratory has synthesized and evaluated the anticancer activity of a number of sulfonylhydrazine DNA modifying agents. As a class, these compounds possess broad spectrum antitumor activity, demonstrating significant activity against a variety of experimental murine tumors, including the P388 and L1210 leukemias, B16 melanoma, M109 lung carcinoma, and M5076 reticulum cell sarcoma, as well as against the human LX-1 lung carcinoma xenograft. The current report describes the activity of a more recently synthesized member of this class, 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylamino)carbonylhydrazine (101M). 101M was active in mice against the i.p. implanted L1210 leukemia over a wide range of doses and produced long-term survivors when administered as a single i.p. bolus of 10, 20, 40, 60, or 80 mg/kg, demonstrating a wider margin of safety than the nitrosourea, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Curative therapy was achieved with doses of 101M that did not produce depression of the bone marrow. 101M was also highly effective against the L1210 leukemia when administered by the oral route. The ability of 101M to penetrate the blood-brain barrier and eradicate leukemia cells in the brain was remarkable (>6 log kill). This agent was also curative against L1210 variants resistant to cyclophosphamide, BCNU, or melphalan. Mice implanted with the murine C26 colon carcinoma were also cured by two injections of 10 or 20 mg/kg of 101M. Administration of 101M by two different well-tolerated regimens caused complete regression of established human glioblastoma U251 xenografts in 100% of treated mice, and significant responses were also obtained with 101M against advanced murine M109 lung carcinomas in mice. The broad spectrum of anticancer activity of the sulfonylhydrazine prodrug 101M coupled with the wide range of therapeutic safety exhibited by this agent, makes 101M particularly attractive for further development and clinical evaluation.

21/7/38 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE


11091179 EMBASE No: 2001109925

Glycation, glycoxidation and carbonyl stress : Role in the vascular complications of Diabetes mellitus

GLICACION, GLICOXIDACION Y ESTRES CARBONILICO: RELEVANCIA EN LAS COMPLICACIONES VASCULARES DE LA DIABETES MELLITUS

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Revista Argentina de Endocrinologia y Metabolismo ( REV. ARGENT. ENDOCRINOL. METAB. ) (Argentina) 2000, 37/3 (141-163)
CODEN: RAEMA ISSN: 0326-4610
DOCUMENT TYPE: Journal ; Article
LANGUAGE: SPANISH SUMMARY LANGUAGE: ENGLISH; SPANISH
NUMBER OF REFERENCES: 124

The post-translational modification of proteins by advanced glycation endproducts (AGE) of the Maillard reaction, is the consequence of a series of non-enzymatic processes involving reactive carbonylic intermediates. To a certain extent, these processes occur physiologically in all body tissues. However, they can be accelerated in conditions that favour substrate stress (by carbohydrates or lipids), oxidative stress and/or insufficient activity of the recently described enzymatic pathways for the detoxification of dicarbonylic compounds. All of these conditions promote the excessive formation of carbonylic AGE precursors. AGE structures contribute to the chemical damage of diverse proteins, and in some cases lead to the formation of irreversible crosslinks. Their tissue levels have been found to increase in an age-dependent manner, and they have been proposed to play a central role in the pathogenesis of a growing number of chronic diseases. In diabetic patients, AGEs accumulate principally on long-lived structural proteins, in a manner that depends on the degree of chronic hyperglycaemia and/or hyperlipidaemia, and which correlates with the presence and severity of vascular complications. This accumulation of Maillard products can induce dysfunctional alterations of the extra-cellular matrix, modifications in the cellular production of cytokines and growth factors due to the specific interaction between AGEs and a family of membrane receptors, and functionally important changes in intracellular proteins. All of these events could be of critical importance in the development and progression of long-term micro- and macrovascular disease associated with Diabetes. Various AGE inhibitors are being developed by the pharmaceutical industry. These compounds have been designed either to irreversibly trap the dicarbonylic AGE precursors, or to chemically break the protein-protein crosslinks typical of certain Maillard structures. AGE inhibitors have been found to delay the development and progression of vasculopathies in diabetic animals. However, their use in humans must await the results of extensive clinical trials currently underway. These results will define the role of AGE inhibitors in the design of strategies aimed at the prevention of vascular abnormalities associated with Diabetes and ageing. They will also allow us to estimate the relative importance of AGE metabolism in the pathophysiology of these human afflictions.

21/7/39 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE


11006463 EMBASE No: 2001052452
Therapeutic targets in radiotherapy
Brown J.M.
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AUTHOR EMAIL: mbrown@leland.stanford.edu
International Journal of Radiation Oncology Biology Physics ( INT. J. RADIAT. ONCOL. BIOL. PHYS. ) (United States) 01 FEB 2001, 49/2 (319-326)
CODEN: IOBPD ISSN: 0360-3016
PUBLISHER ITEM IDENTIFIER: S0360301600014826
DOCUMENT TYPE: Journal ; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

Background: Enormous progress has been made in the past 5 years in our understanding of the gene products governing the response of mammalian cells to ionizing radiation. Many of these are potential targets for enhancing the effectiveness of radiotherapy. However, a major barrier to such efforts is the requirement for a preferential effect on tumor vs. normal cells. Such a requirement can only come about by exploiting a known difference between tumor and normal cells. Methods: This review highlights three differences between tumor and normal cells that are being exploited with fractionated radiotherapy. Results: The three strategies to enhance preferentially tumor response to radiotherapy are inhibition of ras activity using farnesyltransferase inhibitors (FTIs), inhibition of epidermal growth factor receptors (EGFRs), and the use of drugs that preferentially kill hypoxic cells. Each of these strategies exploits a known difference between at least some tumors and their surrounding normal tissues, and each has shown encouraging results when combined with fractionated radiation in preclinical studies. Conclusions: For each of the three strategies to enhance preferentially the sensitivity of cancers, the preclinical and early clinical data are promising for their successful application in radiotherapy. 

21/7/40 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE


10888485 EMBASE No: 2000349487
Use of in vitro methaemoglobin generation to study antioxidant status in the diabetic erythrocyte
Coleman M.D.
Dr. M.D. Coleman, Mechanisms of Drug Toxicity Group, Dept. of Pharmaceutical Sciences, Aston University, Aston Triangle, Birmingham B4 7ET United Kingdom
AUTHOR EMAIL: m.d.coleman@aston.ac.uk
Biochemical Pharmacology ( BIOCHEM. PHARMACOL. ) (United States) 15 NOV 2000, 60/10 (1409-1416)
CODEN: BCPCA ISSN: 0006-2952
PUBLISHER ITEM IDENTIFIER: S0006295200003336
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

Poor glycaemic control in diabetes and a combination of oxidative, metabolic, and carbonyl stresses are thought to lead to widespread non-enzymatic glycation and eventually to diabetic complications. Diabetic tissues can suffer both restriction in their supply of reducing power and

excessive demand for reducing power. This contributes to compromised antioxidant status, particularly in the essential glutathione maintenance system. To study and ultimately correct deficiencies in diabetic glutathione maintenance, an experimental model would be desirable, which would provide in vitro a rapid, convenient, and dynamic reflection of the performance of diabetic GSH antioxidant capacity compared with that of non-diabetics. Xenobiotic-mediated in vitro methaemoglobin formation in erythrocytes drawn from diabetic volunteers is significantly lower than that in erythrocytes of non-diabetics. Aromatic hydroxylamine-mediated methaemoglobin formation is GSH-dependent and is indicative of the ability of an erythrocyte to maintain GSH levels during rapid thiol consumption. Although nitrite forms methaemoglobin through a complex GSH-independent pathway, it also reveals deficiencies in diabetic detoxification and antioxidant performance compared with non-diabetics. Together with efficient glycaemic monitoring, future therapy of diabetes may include trials of different antiglycation agents and antioxidant combinations. Equalization in vitro of diabetic methaemoglobin generation with that of age/sex-matched non-diabetic subjects might provide an early indication of diabetic antioxidant status improvement in these studies. (C) 2000 Elsevier Science Inc.

21/7/41 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE


10759818 EMBASE No: 2000238598
Prostaglandin Einf 2 receptor antagonist (SC-19220) treatment restores the balance to bone marrow burn sepsis
Santangelo S.; Shoup M.; Gamelli R.L.; Shankar R.; Deitch E.A.; Pruitt B.A. Jr.
Dr. R. Shankar, Loyola University Medical Center, Bldg. 110, 2160 S. First Avenue, Maywood, IL 60153 United States
Journal of Trauma - Injury, Infection and Critical Care ( J. TRAUMA INJ. INFECT. CRIT. CARE ) (United States) 2000, 48/5 (826-831)
CODEN: JOTRF ISSN: 1079-6061
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 24

Background: Although prostaglandin Einf 2 (PGEinf 2) has been shown to be immunosuppressive, its role in the development of specific bone marrow myeloid lineages after thermal injury and sepsis has yet to be elucidated. The purpose of this study was to demonstrate that alterations in bone marrow progenitor proliferation favoring monocytopoiesis in burn sepsis can be restored by blocking the cellular interactions of PGEinf 2. Methods: A murine model of burn sepsis with and without treatment with SC-19220, a PGEinf 2 receptor antagonist, was used to determine peripheral monocyte and neutrophil counts as well as the colony forming potential of colony-stimulating factor responsive bone marrow progenitors. Results: Burn sepsis augmented the growth of the early colony-forming unit granulocyte-macrophage and monocyte progenitors and the number of circulating monocytes, whereas granulocyte progenitors and circulating neutrophils demonstrated an opposite response. Treatment with SC-19220 nearly reversed these alterations. Conclusion: These data indicate that abrogating PGEinf 2's actions during burn sepsis can restore the balance in bone marrow granulocyte and monocyte production, further consolidating the

pivotal role PGEinf 2 plays in the pathogenesis of burn sepsis.

21/7/42 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE


10712646 EMBASE No: 2000201523
Pathogenesis and management of dialysis-related amyloid bone disease
Nangaku M.; Miyata T. ; Kurokawa K.
Dr. T. Miyata, Molecular and Cellular Nephrology, Institute of Medical Sciences, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-11 Japan
AUTHOR EMAIL: t-miyata@is.icc.u-tokai.ac.jp
American Journal of the Medical Sciences ( AM. J. MED. SCI. ) (United States) 1999, 317/6 (410-415)
CODEN: AJMSA ISSN: 0002-9629
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 61

Dialysis-related amyloidosis (DRA) is a major complication of chronic renal failure and long-term renal replacement therapy. beta2-Microglobulin is a major constituent of amyloid fibrils in DRA. Amyloid deposition can present as carpal tunnel syndrome, destructive arthropathy, or subchondral bone erosions and cysts. A definitive diagnosis of DRA can only be made using histological findings, but various analytical imaging methods often support diagnosis. Therapy of an established DRA is limited to symptomatic approaches and surgical removal of amyloid deposits. High-flux biocompatible dialysis membranes can be used to delay DRA development. Recent studies have suggested a pathogenic role for a new modification of beta2-microglobulin in DRA. Increased carbonyl compounds modify proteins, which leads to the augmentation of advanced glycation and lipoxidation end products. Thus, uremia might be a state of carbonyl overload with potentially damaging proteins, leading to a new modification of beta2-microglobulin in amyloid fibrils and development of DRA.

21/7/43 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE


10578682 EMBASE No: 2000043505
Inhibition of RAS-targeted prenylation: protein farnesyl transferase inhibitors revisited
Hill B.T.; Perrin D.; Kruczynski A.
B.T. Hill, Division Cancerologie Experimentale, Centre de Recherche Pierre Fabre, 17 Avenue Jean Moulin, 88106 Castres Cedex 06 France
AUTHOR EMAIL: bridget.hill@pierre-fabre.com
Critical Reviews in Oncology/Hematology ( CRIT. REV. ONCOL. HEMATOL. ) ( Ireland) 2000, 33/1 (7-23)
CODEN: CCRHE ISSN: 1040-8428
PUBLISHER ITEM IDENTIFIER: S1040842899000530
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 94

The ras oncogene and its 21 kD protein product, Ras, has emerged during the last decade as a potentially exploitable target for anticancer drug development. The knowledge that Ras was readily prenylated by protein farnesyl transferase (PFTase) and that inhibition of this prenylation had functional consequences for the transformed phenotype that expressed oncogenic Ras provided the rational for the development of PFTase inhibitors. The initial enthusiasm for this approach seemed justified by the early identification of PFTase inhibitors that were able potently and specifically to block Ras processing, signalling and transformation in transformed and tumour cell lines in vitro and in certain selected animal models. More recently the recognition that geranylgeranyl transferase (GGTase) I might also be a therapeutic target is being actively researched. The last couple of years though have proved remarkable with the disclosure of a series of structurally-diverse molecules, whose major in vivo preclinical activites have been well documented against experimental animal tumours, and culminating this year in preliminary reporting of their Phase I clinical evaluations. Nevertheless, during the research and development phases of PFTase inhibitors as pharmaceutical agents for clinical use, there have been several unexpected findings which have raised intriguing and potentially crucial questions about their activities. This review aims to highlight and offer new insights into many of these issues and to bring into perspective concerns arising from basic research, as well as from clinical studies. There seems little doubt that these inhibitors of RAS-targeted prenylation represent a new generation of anticancer drugs for the preclinical researcher, whether they can be successfully exploited in clinical practice should be resolved early in the next millenium. 

21/7/44 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE


10545574 EMBASE No: 2000010985
betainf 2-microglobulin and renal bone disease
Wada T.; Miyata T. ; Sakai H.; Kurokawa K.
T. Miyata, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Kanagawa 259-1193 Japan
Peritoneal Dialysis International ( PERITONEAL DIAL. INT. ) (Canada)
1999, 19/SUPPL. 2 (S413-S416)
CODEN: PDIIE ISSN: 0896-8608
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 21

Dialysis-related amyloidosis (DRA) is characterized by amyloid deposition mainly in bone and joint structures, presenting as carpal tunnel syndrome, destructive arthropathy, and subchondral bone erosions and cysts. betainf 2-microglobulin has been demonstrated to be a major constituent of amyloid fibrils. DRA occurs not only in patients undergoing long-term hemodialysis, but also in patients undergoing continuous ambulatory peritoneal dialysis . The incidence of this complication increases with the duration of dialytic therapy and the age of the patient. While a definitive diagnosis of DRA can be made only by histological findings, various imaging techniques often support diagnosis. The molecular pathogenesis of this complication remains unknown. Recent studies have, however, suggested a pathogenic role of a new modification of betainf 2-microglobulin in amyloid

fibrils - that is, the advanced glycation end-products (AGEs) formed with carbonyl compounds derived from autoxidation of both carbohydrates and lipids (' carbonyl stress'). Therapy for DRA is limited to symptomatic approaches and surgical removal of amyloid deposits. High-flux biocompatible dialysis membranes could be used to delay DRA development.
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File 351:Derwent WPI 1963-2002/UD,UM &UP=200260
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Set     Items   Description
S1        167   AU=MIYATA T? OR AU=MIYATA, T?
S2        701   (PERITONE? OR INRAPERITONE?) (5N) (DIALYS? OR DIALYZ? OR (-
              CARBONYL(5N)STRESS?))
S3         42   CARBONYL(5N) (TRAP? OR INACTIVAT? OR NEUTRALI?)
S4         13   CARBONYL (5N)SCAVENG?
S5        561   AMINOGUANIDINE? ?
S6        135   PYRIDOXAMINE? ?
S7      14099   HYDRAZINE? ?
S8       1126   BIGUANID?
S9        384   SULFHYDRYL
S10     22966   MERCAPTO?
S11      1602   REDUCING(3N)SUGAR? ?
S12         3   S1 AND S2
S13         9   S2 AND (S3-S10)
S14        10   S12 OR S13
?t 14/7/all

 14/7/1
DIALOG(R)File 351:Derwent WPI
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014745922
WPI Acc No: 2002-566629/200260
  Agents for ameliorating carbonyl stress, reducing advanced glycation end
  products and preventing renal failure, comprises cysteamine or its salt
  in cartridge of carbonyl trap or in form of peritoneal dialysate
Patent Assignee: KUROKAWA K (KURO-I); MIYATA T (MIYA-I)
Inventor:  MIYATA T
Number of Countries: 099  Number of Patents: 001
Patent Family:
Patent No     Kind   Date    Applicat No    Kind   Date     Week
WO 200247677   A1  20020620  WO 2001JP10891  A   20011212  200260  B

Priority Applications (No Type Date): JP 2000378112 A 20001212
Patent Details:
Patent No  Kind Lan Pg   Main IPC    Filing Notes
WO 200247677  A1 J  33 A61K-031/145
   Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA
   CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN
   IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM
   PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA
   ZM ZW
   Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR
   IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

Abstract (Basic): WO 200247677 A1
        NOVELTY - Agents for ameliorating carbonyl stress comprises
    cysteamine or its salt.
        DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a
    peritoneal  dialysate  comprising cysteamine or its salt.
        ACTIVITY - Nephrotropic.
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The use of a carbonyl trap containing cysteamine at 5 mM during continuous ambulatory peritoneal dialysis reduced glyoxal and methylglyoxal levels in dialysate to less than 20%.

MECHANISM OF ACTION - None given.

USE - For ameliorating carbonyl stress, reducing advanced glycation end products and preventing renal failure.

pp; 33 DwgNo 0/3

Derwent Class: B05; P34
International Patent Class (Main): A61K-031/145
International Patent Class (Additional): A61K-009/08; A61M-001/28; A61M-001/34; A61P-007/08

14/7/2
DIALOG(R)File 351:Derwent WPI


014531144
WPI Acc No: 2002-351847/200238
Peritoneal dialysate for treating renal failure comprises electrolytic salts, glucose and protein crosslinking inhibitor or protein crosslinkage dissociating agent
Patent Assignee: JAPAN SCI & TECHNOLOGY CORP (NISC-N)
Inventor: NAKAYAMA M; SAKAI A
Number of Countries: 023 Number of Patents: 001
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 200222188 | A1 | 20020321 | WO 2001JP7772 | A | 20010907 | 200238 | B |

Priority Applications (No Type Date): JP 2001186642 A 20010620; JP 2000277810 A 20000913; JP 200140718 A 20010216
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 200222188 | A1 | J | 22 | A61M-001/28 | |

Designated States (National): CA CN KR US
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

Abstract (Basic): WO 200222188 A1

NOVELTY - Peritoneal dialysate (I) comprises electrolytic salts, glucose and a protein crosslinking inhibitor (A) and/or a protein crosslinkage dissociating agent (B).

ACTIVITY - Nephrotropic; Dialysis.

MECHANISM OF ACTION - Antioxidant; Protein crosslinking inhibitor.

In a glycation induced crosslinking model, peritoneal dialysate containing human albumin (50 mg/ml), glucose (20 mM/l) and N-acetylcysteine (20 mM/l), showed 7% crosslinking compared to 100% for a control without N-acetylcysteine after 2 weeks at 37degreesC.

USE - For treating renal failure.

ADVANTAGE - Prevents and/or dissociates protein crosslinking due to oxidation and/or denaturation of glucose, preventing hardening of peritoneal tissue and allowing dialysis to continue.

pp; 22 DwgNo 0/0

Derwent Class: B04; P34
International Patent Class (Main): A61M-001/28

14/7/3

DIALOG(R)File 351:Derwent WPI


014140750 **Image available**
WPI Acc No: 2001-624961/200172
Neutralization of microorganisms in fluids e.g. blood involves addition of a microorganism neutralizer to the fluid and exposing the fluid to a triggering agent
Patent Assignee: GOODRICH R P (GOOD-I); PLATZ M S (PLAT-I)
Inventor: GOODRICH R P; PLATZ M S
Number of Countries: 001 Number of Patents: 001
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week |
|---|---|---|---|---|---|---|
| US 20010024781 | A1 | 20010927 | US 99420652 | A | 19991019 | 200172 B |
| | | | US 2001777727 | A | 20010205 | |

Priority Applications (No Type Date): US 2001777727 A 20010205; US 99420652 A 19991019
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| US 20010024781 | A1 | | 22 | A61K-031/495 | CIP of application US 99420652<br>CIP of patent US 6268120 |

Abstract (Basic): US 20010024781 A1

NOVELTY - Neutralization of microorganisms in fluids or on surfaces involves adding to the fluid or applying to the surface, a microorganism neutralizer and exposing the fluid or surface to a triggering agent.

DETAILED DESCRIPTION - Neutralization of microorganisms in fluids or on surfaces involves adding to the fluid or applying to the surface, a microorganism neutralizer of formula (I) (excluding compounds of formula Ia and Ib) and exposing the fluid or surface to a triggering agent. The fluid contains at least one components selected from protein, blood or blood constituent.

R1-R6=T, T' or NRa-(CRbRc)n-X;

T=H, (1-20C) -alkyl, -alkenyl, -alkynyl or -aryl (optionally substituted with at least one of -O-, -S- or T'), 5-6C straight chain or a cyclic saccharide of formula (i) or amino acid groups;

T'=-OH, NH2, -SO4, -PO4 or X;

X=Cl, Br or I;

Ra, Rb, Rc=T or their salts or X;

n=0-20;

R'a, R'b, R'c=H, optionally substituted hydrocarbyl or X; and

W=water soluble group;

provided that R1 is not H, -OH or a straight chain alkyl where the second carbon of the chain is substituted with -OH or=O and when R2, R3 and R6=H then R1, R4 and R5 are not all methyl, except when (I) is a compound of formula (Ic) or (Id).

An INDEPENDENT CLAIM is also included for a non-toxic composition comprising a blood product additive photosensitizer of formula (I) (excluding compounds (I; R2, R3, R6=H; R1, R4=Me; R5=COOR), (I; R2, R3, R6=H; R1, R5=Me; R4=COOR) or (Ib).

R=H or optionally substituted 1-20C alkyl;

provided that: when R2, R3 and R6 are H, and R4 and R5 are CH3, then R1 is not a 2-5C alkyl (terminating in -OH, -COH, or -H), -OH, a straight chain allyl group substituted on the second carbon with -OH,=O, -CH2CH2-(CHOH)2-CH3, -CH2CH2-(CHOH)2-CH2SO4, 1'-D-sorbityl,

1'-D-dulcityl, 1'-D-rhamnityl, 1'-D,L-glyceryl, -CH2-O-C(O)-CH3, -CH2-O-C(O)-CH2CH3, 2', 3', 4', 5'di-O-isopropyridene-riboflavin or 8-aminooctyl; when R4 and R5 are Cl and R2, R3 and R6 are H, then R1 is not 1'-D sorbityl or 1'-D-dulcityl. When R1 and R4 are methyl and R2, R3 and R6 are H, R5 is not ethyl or Cl; when R1 is CH3 and R2, R3 and R6 are H, then R4 and R5 are not tetramethylene or methoxy; when R1, R4 and R5 are CH3 and R3 and R6 are H, then R2 is not -CH2CH2NH or 4-substituted morpholine; when R4 is methoxy and R1 is ethyl-2'N-pyrrolidino and R2, R3, and R6 are H, then R5 is not Cl; when R5 is Cl or methyl and R2 - R4 and R6 are H, then R1 is not N,N-dimethylaminopropyl or N,N-diethylaminoethyl; when R6 is -NH2 and R1, R2, R4 and R5 are H, then R3 is not -NH(CH2CH2)Cl; when R2, R3 and R6 are H, then R1, R4, R5 are not all methyl groups; when R3 and R6 are H, then R1, R4, R5 and R2 are not methyl; when R1, R4 and R5 are methyl and R3 and R6 are H, then R2 is not carboxymethyl; when R1 and R5 are methyl and R2, R3 and R6 are H, then R4 is not -NH2; when R4 and R5 are methyl and R2, R3 and R6 are H, then R1 is not a phenyl; when R2 - R6 are H, then R1 is not methyl or N,N-dimethylaminoethyl; when R1 is acetoxyethyl and R3 and R6 are H, then R2, R4, R5 are not methyl; when R1 is N,N-diethylaminoethyl and R2, R3, R4 and R6 are H, then R5 is not methyl; when R1 is methyl and R2, R3 and R6 are H, then R4 and R5 are not Cl; when R5 is NH2 and R2 - R4 and R6 are H, then R1 is not ethyl, beta-chloroethyl, n-butyl, anilino, benzyl, phenyl, p-tolyl or p-anisyl. When R1 is N,N-dimethylaminopropyl and R2, R3, R5 and R6 are H, then R4 is not Cl; when R5 is CH3, then R4 is not -OH, -Br, -Cl, -SH, -O-Alk, or -Salk; when R1 is Alk or H (in which Alk is an 1-4C alkyl), then R6, R3 and R2 are H; when R1, R3, R6 are H and R4 and R5 are methyl, then R2 is not a 11C straight chain alkyl group, octadecyl or undecyl; when R1, R4 and R5 are methyl, and R3 and R6 are H, then R2 is not a benzyl; R1 or R2 do not contain a poly(pyrrolecarboxamide) group; when R2 is H, methyl, hydroxyethyl or benzyl and R3 and R6 are H and R1 is ethyl, propyl, isopropyl, butyl, pentyl, hexyl, phenyl, benzyl, phenethyl, naphthyl, p-tolyl, p-ethylphenyl, p-anisyl, p-ethoxyphenyl, p-butoxyphenyl, 3,4-dicholorophenyl, methoxyethyl or ethoxyethyl, then R5 is not bromo, chloro, nitro or trifluoromethyl. R1 is not a 5C allyl in which four carbons are substituted with -O-COR in which RCO is a straight chain 4-20C alkanoyl; when R2 - R6 are H, then R1 is not a phosphoric acid substituted hydroxyalkyl; R1 is not a 2-6 member alkyl chain terminated with a sulfate radical, a phosphate radical or an acyloxy radical, the acyl group of which is derived from an organic acid with not more than 18C atoms.

ACTIVITY - Antibacterial.

No biological data given.

MECHANISM OF ACTION - None given.

USE - For treating a fluid (preferably food product, a drink for human or animal consumption or peritoneal dialysis solution) or a surface (preferably a food surface, surface of the animal carcass, a bathing or washing vessel, food preparation surface, wound surface) to neutralize microorganisms selected from bacteria, bacteriophages, and intracellular and extracellular viruses such as HIV viruses, hepatitis virus, sindbis virus, cytomegalovirus, vesicular stomatitis virus, herpes simplex virus, vaccinia virus, human T-lymphotropic retrovirus, HTLV-III, lymphadenopahy virus LAV/IDAV, parvovirus, transfusion-transmitted virus, Epstein-Barr virus, bacteriophages thetaX174, theta6, lambda, R17, T4, T2, P.aeruginosa, S.aureus, S.epidermidis, L. monocytogenes, E.coli, K pneumoniae, and S. marcescens.

ADVANTAGE - If the neutralizer produces photolytic products they are of low or no toxicity to humans or animals. The neutralizer does not destroy desired components of the fluid being contaminated, and does not degrade into products which substantially destroy desired components or have significant toxicity or decompose into ultraviolet light absorbing compounds.

pp; 22 DwgNo 0/0

Derwent Class: B02

International Patent Class (Main): A61K-031/495

International Patent Class (Additional): C07D-239/70

14/7/4

DIALOG(R)File 351:Derwent WPI



013933763

WPI Acc No: 2001-417977/200144

Carbonyl stress-ameliorating agents containing an enzyme with glyoxalase I activity as the active ingredient for rapid elimination of carbonyl compounds originated from sugars and lipids with high specificity, e.g. to treat renal failure

Patent Assignee: KUROKAWA K (KURO-I); MIYATA T (MIYA-I)

Inventor: MIYATA T

Number of Countries: 093 Number of Patents: 002

Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 200145733 | A1 | 20010628 | WO 2000JP8911 | A | 20001215 | 200144 | B |
| AU 200118919 | A | 20010703 | AU 200118919 | A | 20001215 | 200164 | |

Priority Applications (No Type Date): JP 99360479 A 19991220

Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 200145733 | A1 | J | 37 | A61K-038/51 | |

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

| | | | | |
|---|---|---|---|---|
| AU 200118919 | A | | A61K-038/51 | Based on patent WO 200145733 |

Abstract (Basic): WO 200145733 A1

NOVELTY - Carbonyl stress-ameliorating agents contain an enzyme with glyoxalase I activity and carbonyl compound reductant as active ingredients. These agents allow carbonyl compounds to be rapidly eliminated with high specificity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method for eliminating carbonyl compounds comprising contacting the blood of a patient or peritoneal dialyzate with a support immobilized with an enzyme having glyoxalase I activity in the presence of a carbonyl compound reductant;

(2) peritoneal dialyzate containing the carbonyl stress -ameliorating agent; and

(3) a method for ameliorating carbonyl stress , comprises contacting peritoneal dialyzate with an enzyme having glyoxalase I

activity in the presence of a carbonyl compound reductant.
ACTIVITY - Nephrotropic
MECHANISM OF ACTION - Carbonyl compound reductant.
USE - The agents are useful for the rapid elimination of carbonyl compounds originated from sugars and lipids with high specificity to relieve carbonyl stress conditions, e.g. to treat renal failure.
ADVANTAGE - Carbonyl compounds can be rapidly eliminated with high specificity.
pp; 37 DwgNo 0/6
Derwent Class: B04; D16; P34
International Patent Class (Main): A61K-038/51
International Patent Class (Additional): A61K-038/06; A61K-038/46; A61K-045/00; A61M-001/16; A61M-001/28; A61P-007/08; A61P-043/00

14/7/5
DIALOG(R)File 351:Derwent WPI


013832009 **Image available**
WPI Acc No: 2001-316221/200133
Neutralization of microorganisms in fluids e.g. blood, involves adding an isoalloxazine derivative as neutralizer and exposing fluid to triggering event
Patent Assignee: GAMBRO INC (GAMB ); GOODRICH R P (GOOD-I); PLATZ M S (PLAT-I)
Inventor: GOODRICH R P; PLATZ M S
Number of Countries: 095 Number of Patents: 004
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 200128599 | A1 | 20010426 | WO 2000US25213 | A | 20000915 | 200133 | B |
| US 6268120 | B1 | 20010731 | US 99420652 | A | 19991019 | 200146 | |
| AU 200075807 | A | 20010430 | AU 200075807 | A | 20000915 | 200148 | |
| EP 1221982 | A1 | 20020717 | EP 2000965012 | A | 20000915 | 200254 | |
| | | | WO 2000US25213 | A | 20000915 | | |

Priority Applications (No Type Date): US 99420652 A 19991019
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 200128599 | A1 | E | 47 | A61L-002/08 | |

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

| | | | | |
|---|---|---|---|---|
| US 6268120 | B1 | | A01N-001/02 | |
| AU 200075807 | A | | A61L-002/08 | Based on patent WO 200128599 |
| EP 1221982 | A1 | E | A61L-002/08 | Based on patent WO 200128599 |

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): WO 200128599 A1
NOVELTY - Neutralization of microorganisms present in a fluid involves adding isoalloxazine derivatives as a neutralizer to the fluid, and exposing the fluid to a triggering event.
DETAILED DESCRIPTION - Neutralization of microorganisms present in

a fluid or a surface involves adding/applying a neutralizer to the fluid/surface and exposing the fluid/surface to a triggering event. The neutralizer is of formula (I).

R1 - R6=H, optionally substituted hydrocarbyl, alcohol, (poly)amine, sulfate, phosphate, chlorine, bromine, iodine (their salts) or -NRa-(CRbRc)n-X;

X=chlorine, bromine or iodine;

Ra, Rb and Rc=H, optionally substituted hydrocarbyl, chlorine, bromine or iodine;

n=0 - 20.

Provided that when R2, R3 and R6 are hydrogen, then R1 is not -OH or a straight chain alkyl containing the second carbon substituted with -OH or O, and R1, R4 and R5 are not methyl.

INDEPENDENT CLAIMS are also included for:

(1) a compound of formula (I) with the provision that:

(a) when R4 and R5 are CH3, and R2, R3 and R6 are H, then R1 is not -OH, a straight chain alkyl containing second carbon substituted with -OH or O, 2-5C straight chain alkyl terminating in -OH, -COH or -H, -CH2CH2-(CHOH)2-CH3, -CH2CH2-(CHOH)2, -CH2SO4, 1'-D-sorbityl, 1'-D-dulcityl, 1'-D-rhamnityl, 1'-D,L-glyceryl, -CH2-O-C(O)-CH3, -CH2-O-C(O)-CH2CH3, 2',3',4',5'-di-O-isopropylideneriboflavin or 8-aminooctyl;

(b) when R4 and R5 are chlorine, and R2, R3 and R6 are H, then R1 is not 1'-D-sorbityl or 1'-D-dulcityl;

(c) When R1 and R4 are methyl, and R2, R3 and R6 are H, then R5 is not ethyl or chloro;

(d) When R1 is methyl and R2, R3 and R6 are H, then R4 and R5 are not methoxy or tetramethylene simultaneously;

(e) When R1, R4 and R5 are CH3; R3 and R6 are H, then R2 is not -CH2CH2NH. When R1, R4 and R5 are CH3; R3 and R6 are H, then R2 is not morpholinyl;

(f) when R4 is methoxy, R1 is ethyl-2'N-pyrrolidino, and R2, R3 and R6 are H, then R5 is not chloro;

(g) When R5 is chloro or methyl, and R2, R3, R4 and R6 are H, then R1 is not N,N-dimethylaminopropyl or N,N-diethylaminoethyl;

(h) When R6 is -NH2 and R1, R2, R4 and R5 are H, then R3 is not -NH(CH2CH2)Cl;

(i) When R2, R3 and R6 are H, then R1, R4, and R5 are not methyl simultaneously;

(j) When R3 and R6 are H, then R1, R4, R5 and R2 are not methyl simultaneously;

(k) When R3 and R6 are H, and R1, R4 and R5 are methyl, then R2 is not carboxymethyl;

(l) When R1 and R5 are methyl, and R2, R3 and R6 are H, then R4 is not -NH2;

(m) When R4 and R5 are methyl, and R2, R3 and R6 are H, then R1 is not phenyl;

(n) When R2 - R6 are H, then R1 is not methyl or N,N-dimethylaminoethyl. When R3 and R6 are H, and R1 is acetoxyethyl, then R2, R4 and R5 are not methyl simultaneously;

(o) When R1 is N,N-diethylaminoethyl, and R2, R3, R4 and R6 are H, then R5 is not methyl;

(p) When R1 is methyl, and R2, R3 and R6 are H, then R4 and R5 are not chlorine simultaneously;

(q) When R5 is NH2, and R2, R3, R4 and R6 are H, then R1 is not ethyl, beta-chloroethyl, n-butyl, anilino, benzyl, phenyl, p-tolyl or p-anisyl; and

(r) When R1 is N,N-dimethylaminopropyl and R2, R3, R5 and R6 are H, then R4 is not chlorine;

(2) preparation of a compound of formula (III) involves:

(i) contacting (II) with sodium azide;

(ii) reacting product of step (1) with ethylene oxide and POCl3; and

(iii) reacting the product of step (2) with a water solubilizing group; and

(3) preparation of a compound of formula (II) involves:

(i) photolyzing carboxyriboflavin;

(ii) reacting the product of step (i) with oxallylchloride; and

(iii) reacting the product of step (ii) with ascorbate, glucosamine, protected glucose derivative, diethylene glycol or triethylene glycol.

W=water soluble group.

USE - The method is useful for treating fluids e.g. whole blood, separated blood product (particularly platelets, red blood cells, serum, plasma), therapeutic protein composition, biological active protein (particularly factor VIII, Von Willebrand factor, factor IX, factor X, factor XI, Hageman factor, prothrombin, anti-thrombin III, fibronectin, plasminogen, plasma protein fraction, peritoneal dialysis solutions, immune serum globulin, modified immune globulin, albumin, plasma growth hormone, somatomedin, plasminogen streptokinase complex, ceruloplasmin, transferrin, haptoglobin, antitrypsin and prekallikrein), for treating a food surface, the surface of an animal carcass, a food-preparation surface, a surface of a bathing or washing vessel and a wound surface (all claimed).

ADVANTAGE - The neutralizer produces photolytic products which are of low or no toxicity to humans or animals.

pp; 47 DwgNo 0/0

Derwent Class: B02; D13; D22; E13; P34
International Patent Class (Main): A01N-001/02; A61L-002/08
International Patent Class (Additional): A61K-031/525; A61L-002/10; C07D-471/14; C07D-475/14

14/7/6
DIALOG(R)File 351:Derwent WPI


013065679
WPI Acc No: 2000-237551/200020
Drug for use in peritoneal dialysates for relieving carbonyl stress comprise carbonyl compound trapping agent
Patent Assignee: KUROKAWA K (KURO-I); MIYATA T (MIYA-I)
Inventor: MIYATA T
Number of Countries: 089 Number of Patents: 007
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 200010606 | A1 | 20000302 | WO 99JP4521 | A | 19990823 | 200020 | B |
| AU 9953045 | A | 20000314 | AU 9953045 | A | 19990823 | 200031 | |
| NO 200100931 | A | 20010423 | WO 99JP4521 | A | 19990823 | 200130 | |
| | | | NO 2001931 | A | 20010223 | | |
| EP 1108434 | A1 | 20010620 | EP 99938581 | A | 19990823 | 200135 | |
| | | | WO 99JP4521 | A | 19990823 | | |
| JP 2000565926 | X | 20011030 | WO 99JP4521 | A | 19990823 | 200204 | |
| | | | JP 2000565926 | A | 19990823 | | |

KR 2001072888 A 20010731 KR 2001702299 A 20010223 200209
CN 1324248 A 20011128 CN 99812545 A 19990823 200219

Priority Applications (No Type Date): JP 99155393 A 19990602; JP 98237108 A 19980824
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
WO 200010606 A1 J 78 A61K-045/00
Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
AU 9953045 A A61K-045/00 Based on patent WO 200010606
NO 200100931 A A61K-000/00
EP 1108434 A1 E A61K-045/00 Based on patent WO 200010606
Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2000565926 X A61K-045/00 Based on patent WO 200010606
KR 2001072888 A A61K-031/44
CN 1324248 A A61K-045/00

Abstract (Basic): WO 200010606 A1
NOVELTY - Drug comprise a carbonyl compound trapping agent.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a cartridge for trapping carbonyl compounds which comprises a trapping agent which inactivates or destroys compounds formed and accumulated during peritoneal dialysis .
ACTIVITY - Cardiovascular-Gen.; endocrine-Gen.
In a glucose decomposition production assay, using IGS rat peritoneal cells, methyl glyoxal at 400 micro-M significantly increased (p is less than 0.0005) the VEGF/G3PHD signal measured.
MECHANISM OF ACTION - Maillard reaction inhibitor.
USE - Used as carbonyl compound trapping agents for relieving carbonyl stress in the peritoneal cavity. Trapping agents can be used to treat dialysates before use in dialysis to remove carbonyl compounds formed during sterilization and storage or can be administered directly to patients to eliminate carbonyl compounds originating in the blood which flow into the peritoneal cavity as dialysis proceeds. Trapping agents thus prevent modification of proteins and inhibit peritoneal damage associated with dialysis .
pp; 78 DwgNo 0/27
Derwent Class: B05; P34
International Patent Class (Main): A61K-000/00; A61K-031/44; A61K-045/00
International Patent Class (Additional): A61K-031/15; A61K-031/155; A61K-031/195; A61K-033/44; A61K-038/16; A61K-038/38; A61M-001/28; A61P-013/12

14/7/7
DIALOG(R)File 351:Derwent WPI


013010694 **Image available**
WPI Acc No: 2000-182546/200016
Treating a fluid containing protein, blood and/or blood constituents to

inactivate microorganisms comprises adding endogenous photosensitizer and exposing to photoradiation

Patent Assignee: GAMBRO INC (GAMB ); COBE LAB INC (COBE-N)

Inventor: CORBIN F; GOODRICH R P; HLAVINKA D; WOOD E C

Number of Countries: 087 Number of Patents: 016

Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 200004930 | A2 | 20000203 | WO 99US16404 | A | 19990721 | 200016 | B |
| AU 9952198 | A | 20000214 | AU 9952198 | A | 19990721 | 200029 | |
| NO 200001440 | A | 20000519 | WO 99US16404 | A | 19990721 | 200035 | |
| | | | NO 20001440 | A | 20000320 | | |
| CZ 200001406 | A3 | 20000913 | WO 99US16404 | A | 19990721 | 200054 | |
| | | | CZ 20001406 | A | 19990721 | | |
| EP 1047458 | A2 | 20001102 | EP 99937340 | A | 19990721 | 200056 | |
| | | | WO 99US16404 | A | 19990721 | | |
| ZA 200001357 | A | 20001227 | ZA 20001357 | A | 20000316 | 200103 | |
| SK 200000583 | A3 | 20010118 | WO 99US16404 | A | 19990721 | 200108 | |
| | | | SK 2000583 | A | 19990721 | | |
| HU 200004907 | A2 | 20010528 | WO 99US16404 | A | 19990721 | 200140 | |
| | | | HU 20004907 | A | 19990721 | | |
| CN 1287496 | A | 20010314 | CN 99801588 | A | 19990721 | 200141 | |
| US 6258577 | B1 | 20010710 | US 98119666 | A | 19980721 | 200141 | |
| US 6277337 | B1 | 20010821 | US 98119666 | A | 19980721 | 200150 | |
| | | | US 99357188 | A | 19990720 | | |
| KR 2001015594 | A | 20010226 | KR 2000702971 | A | 20000321 | 200156 | |
| BR 9906622 | A | 20011218 | BR 996622 | A | 19990721 | 200209 | |
| | | | WO 99US16404 | A | 19990721 | | |
| AU 744978 | B | 20020307 | AU 9952198 | A | 19990721 | 200229 | |
| MX 2000002800 | A1 | 20010901 | MX 20002800 | A | 20000320 | 200239 | |
| AU 200245838 | A | 20020725 | AU 200245838 | A | 20020606 | 200260 | N |

Priority Applications (No Type Date): US 99357188 A 19990720; US 98119666 A 19980721; AU 200245838 A 20020606

Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 200004930 | A2 | E | 94 | A61L-002/00 | |
| Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW | | | | | |
| Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW | | | | | |
| AU 9952198 | A | | | A61L-002/00 | Based on patent WO 200004930 |
| NO 200001440 | A | | | A61L-000/00 | |
| CZ 200001406 | A3 | | | A61L-002/00 | Based on patent WO 200004930 |
| EP 1047458 | A2 | E | | A61L-002/00 | Based on patent WO 200004930 |
| Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI | | | | | |
| ZA 200001357 | A | | 96 | A61L-000/00 | |
| SK 200000583 | A3 | | | A61L-002/00 | |
| HU 200004907 | A2 | | | A61L-002/00 | Based on patent WO 200004930 |
| CN 1287496 | A | | | A61L-002/00 | |
| US 6258577 | B1 | | | C12N-013/00 | |
| US 6277337 | B1 | | | B01J-019/08 | CIP of application US 98119666 |
| KR 2001015594 | A | | | A61L-002/00 | |
| BR 9906622 | A | | | A61L-002/00 | Based on patent WO 200004930 |
| AU 744978 | B | | | A61L-002/00 | Previous Publ. patent AU 9952198 |

Based on patent WO 200004930

MX 2000002800 A1 A61L-002/00
AU 200245838 A A61L-002/00 Div ex patent AU 744978

Abstract (Basic): WO 200004930 A2

NOVELTY - Treating a fluid containing protein, blood and/or blood constituents to inactivate microorganisms within the fluid comprises:

(a) adding inactivation-effective, substantially non-toxic amount of an endogenous photosensitizer or an endogenously based derivative photosensitizer to the fluid; and

(b) exposing the fluid to photoradiation sufficient to activate the photosensitizer.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method for treating a fluid to inactivate microorganisms within the fluid comprising steps (a) and (b) as above;

(2) a fluid comprising biologically active protein, blood or blood constituents, and photosensitizer or its photoproduct made as above;

(3) a fluid as in (2) also containing an enhancer;

(4) a system (I) for treating a fluid to inactivate microorganisms which may be present in the fluid;

(5) a system (2) for inactivation of microorganisms in a fluid containing microorganisms;

(6) a system (3) for treating a fluid to inactivate microorganisms which may be present in the fluid;

(7) a method for inactivating microorganisms on surfaces;

(8) a method for treating a fluid to inactivate microorganisms which may be present in the fluid, the fluid containing a component selected from protein, blood and blood constituents without destroying the biological activity of the component, the method comprising adding an inactivation-effective, non-toxic amount of vitamin K5 to the fluid to substantially inactivate the microorganisms;

(9) a method of treating a surface to inactivate microorganisms which may be present on it or which may come into contact with it, the method comprising coating the surface with an inactivation-effective, non-toxic amount of vitamin K5 to substantially inactivate the microorganisms;

(10) an aqueous platelet additive solution comprising an endogenous photosensitizer selected from endogenous alloxazines, K vitamins and vitamin L;

(11) a method for treating a fluid to inactivate white blood cells which may be present in the fluid.

ACTIVITY - Antibacterial; antiviral.

Platelet concentrate was mixed with platelet additive solution Isolyte S (20:80) to produce 'test medium'. Test medium and plasma (platelet concentration without platelet additive solution) were spiked with (1) S. aureus, (2) S. epidermidis, (3) L. monocytogenes and (4) Escherichia coli. Vitamin K5 (300 mug/ml) was added to each and the solutions irradiated at energy levels of 30 and 60 J/cm2. Inactivation as function of energy irradiation at 0 J/cm2 was: (1) 4.3, (2) 2.6, (3) 2.8 and (4) 3.5; 30 J/cm2 was: (1) 3.6, (2) 2.7, (3) 2 and (4) 2; and 60 J/cm2 was: (1) 3.2, (2) 2.5, (3) 1 and (4) 1.

MECHANISM OF ACTION - Replication inhibitor.

USE - Used to inactivate biological contaminants. Used to treat fluids containing proteins, blood and/or blood constituents such as separated blood product or platelets, red blood cells, serum or plasma separated from whole blood to inactivate microorganisms including whole blood, food products, drinks for human or animal consumption and

peritoneal fluid such as water, fruit, juices, milk, broths and soups as well peritoneal and parenteral solutions. Used to produce blood products. Used to treat fluids to inactivate microorganisms including those on surfaces and to treat fluid to inactivate white blood cells such as to treat food surfaces such as fruit, vegetables, animal carcasses and surfaces of cut or processed foods. Used to decontaminate surfaces of bathing or washing vessels such as kitchen sink, bathtub, hot tub, swimming pool, living animals or plants and wound surfaces.

ADVANTAGE - Endogenous photosensitizers are not inherently toxic and do not yield photoproducts after photoradiation, no removal or purification step is required after decontamination and treated product can be returned directly to patient's body or administered to patient requiring its therapeutic effect. Mixtures of visible and ultraviolet light do not damage platelets, but reduce amount of harmful ultraviolet light required. The methods do not destroy the desired components of the fluid.

DESCRIPTION OF DRAWING(S) - Inactivation of bacteria in platelet preparations using vitamin K5 as photosensitizer as function of energy of irradiation.

pp; 94 DwgNo 8/23

Derwent Class: B04; B05; D13; D22; E19; P34
International Patent Class (Main): A61L-000/00; A61L-002/00; B01J-019/08; C12N-013/00
International Patent Class (Additional): A01N-001/02

14/7/8
DIALOG(R)File 351:Derwent WPI


010391779
WPI Acc No: 1995-293093/199538
New additive system useful for polyvinyl chloride formulation - comprises organo-tin cpd. prim. and polyepoxide sec. stabilisers and polyethylene@ external lubricant for prepn. of medical prod. for stability
Patent Assignee: BAXTER INT INC (BAXT )
Inventor: BUAN A L; LAURIN D; BAUN A L
Number of Countries: 023 Number of Patents: 006
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| WO 9521885 | A1 | 19950817 | WO 95US1416 | A | 19950203 | 199538 | B |
| ZA 9501041 | A | 19951227 | ZA 951041 | A | 19950209 | 199605 | |
| EP 694052 | A1 | 19960131 | EP 95909462 | A | 19950203 | 199609 | |
| | | | WO 95US1416 | A | 19950203 | | |
| JP 8509022 | W | 19960924 | JP 95521268 | A | 19950203 | 199704 | |
| | | | WO 95US1416 | A | 19950203 | | |
| US 5643501 | A | 19970701 | US 92889550 | A | 19920527 | 199732 | |
| | | | US 94194742 | A | 19940209 | | |
| CN 1123033 | A | 19960522 | CN 95190075 | A | 19950203 | 199746 | |

Priority Applications (No Type Date): US 94194742 A 19940209; US 92889550 A 19920527
Cited Patents: EP 295534; US 4039486; WO 9324563
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| WO 9521885 | A1 | E | 33 | C08K-005/00 | |

Designated States (National): CA CN JP KR

Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

| | | | | |
|---|---|---|---|---|
| ZA 9501041 | A | 30 | C07G-000/00 | |
| EP 694052 | A1 E | | | Based on patent WO 9521885 |
| Designated States (Regional): AT BE CH DE ES FR GB IT LI NL SE | | | | |
| JP 8509022 | W | 25 | C08L-027/06 | Based on patent WO 9521885 |
| US 5643501 | A | 7 | C09K-015/06 | CIP of application US 92889550 |
| CN 1123033 | A | | C08K-005/00 | |

Abstract (Basic): WO 9521885 A

Additive system for polyvinyl chloride (PVC) formulation for improving processability while maintaining thermal stability of the formulation comprises:

(a) a primary stabiliser (PS) which is a Lewis acid metal cpd. selected from organo tin and organo zinc cpds.;

(b) a secondary stabiliser (SZ) comprising epoxide cpds. having less than 5.2 oxirane gps. per molecule; and

(c) an external lubricant (EL).

The ratio of (a):(b) maximises thermolytic colour stability while limiting generation of excessive build up, plate out and dark particles during the processing of the PVC formulation.

Also claimed is an additive system comprising 0.02-0.5 parts prim. stabiliser.

Also claimed is a medical prod. (MP) produced from a PVC formulation having an additive system (AS) comprising:

(i) 0.06 wt.% (a);

(ii) 9.1 wt.% (b); and

(iii) 0.015 wt.% (c).

USE - The PVC formulations have medical use pref. for sterilisable medical derivs. esp. i.v. and drug delivery containers, dialysis containers, blood bags, soln. admin. sets, tubing and other moulded articles.

ADVANTAGE - The additive systems may be used for rigid, semi-rigid or flexible PVC applications. They provide stability and processability to low or non-plasticised PVC formulations which may be injection moulded to produce rigid or semi rigid prods. such as filter housings, medical drip chambers and containers, and to plasticised PVC formulations typically used to produce flexible medical containers and tubing for fluids such as i.v. solns., peritoneal dialysis solns., blood and blood prods.

The PVC formulations are functional over a wide temp. range even in excess of the Tg of the compsn. They may be steam sterilised at 121 deg. C without causing extractability, water-blush haze, colour, haze and particle generations that are required for medical use. The medical containers, ports and tubing have lower extractables and improved transparency after steam sterilisation.

Dwg.0/0

Abstract (Equivalent): US 5643501 A

An additive system, for a polyvinyl chloride formulation for improved processability while maintaining thermal stability of the formulation, consists essentially of a primary stabiliser of a Lewis acid metal compound selected from a dialkyl tin ester, a di (n-octyl) tin maleate polymer and a di (n-octyl) tin-S,S'-bis (isooctyl) mercapto -acetate in an amount of 0.02-0.5 parts per one hundred parts of the polyvinyl chloride; a secondary stabiliser selected from epoxide compounds having less than 5.2 oxirane groups per molecule, in an amount of 5-100 parts per one hundred parts of the polyvinyl chloride;

an effective amount of an external lubricant for lubrication of the polyvinyl chloride formulation; where the ratio of the primary stabiliser to the secondary stabiliser limits extractables and generating build-up and plate-out during processing of the formulation; and where the formulation has a water blush haze of less than 6% on a film 15 mils thick after autoclaving the formulation.

Dwg.0/0

Derwent Class: A14; A17; A28; A96; E12; P34
International Patent Class (Main): C07G-000/00; C08K-005/00; C08L-027/06; C09K-015/06
International Patent Class (Additional): A61L-027/00; A61L-031/00; C08F-000/00; C08K-005/05; C08K-005/098; C08K-005/15; C08K-005/57; C08L-023/02; C08L-025/00; C08L-027/12; C08L-033/00; C08L-035/00; C08L-081/00; C09K-015/10; C08K-005/00; C08K-005-09; C08K-005-15; C08K-005-56

14/7/9
DIALOG(R)File 351:Derwent WPI


008668313
WPI Acc No: 1991-172334/199124
Aq. dialysis and rinsing soln. for intra- peritoneal use - contg. electrolytes and alpha-keto-carboxylic acids as osmotic substance
Patent Assignee: NEPHRO-MEDICA PHARM (NEPH-N); NEPHRO-MEDICA PHARM VERTRIEBSGESELLSCHAF (NEPH-N)
Inventor: GRETZ N
Number of Countries: 015 Number of Patents: 007
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| DE 3940052 | A | 19910606 | DE 3940052 | A | 19891204 | 199124 | B |
| EP 431465 | A | 19910612 | EP 90122823 | A | 19901129 | 199124 | |
| WO 9108009 | A | 19910613 | | | | 199126 | |
| DE 3940052 | C | 19911205 | | | | 199149 | |
| EP 431465 | B1 | 19940413 | EP 90122823 | A | 19901129 | 199415 | |
| DE 59005355 | G | 19940519 | DE 505355 | A | 19901129 | 199421 | |
| | | | EP 90122823 | A | 19901129 | | |
| ES 2054200 | T3 | 19940801 | EP 90122823 | A | 19901129 | 199432 | |

Priority Applications (No Type Date): DE 3940052 A 19891204
Cited Patents: EP 54635
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| EP 431465 | A | | | | |
| Designated States (Regional): AT BE CH DE ES FR GB GR IT LI NL SE | | | | | |
| WO 9108009 | A | | | | |
| Designated States (National): JP US | | | | | |
| EP 431465 | B1 | G | 14 | A61K-033/00 | |
| Designated States (Regional): AT BE CH DE DK ES FR GB GR IT LI NL SE | | | | | |
| DE 59005355 | G | | | A61K-033/00 | Based on patent EP 431465 |
| ES 2054200 | T3 | | | A61K-033/00 | Based on patent EP 431465 |

Abstract (Basic): DE 3940052 A

Aq. dialysis and rinsing soln. for intraperitoneal use contains (A) electrolytes in osmotic blood-compatible amts. (B) outer osmotically effective substances e.g. physiologically metabolisable alpha

ketocarboxylic acid(s) chosen from alpha-ketoglutarate, pyruvate, alpha-ketosuccinate, alpha- or 3-methyl-alpha- ketoadipate, 3-,4 -methyl-alpha-ketovalerianate, 3-phenyl or mercapto -pyruvate, pref. alpha-ketoglutarate, pyruvate or alpha-ketosuccinate in a concn. of 1-70 g/l and (1) opt. other additives, and has an osmotic pressure of 300-700 mosm/l.

USE/ADVANTAGE - Solns. can be used in the long-term treatment of patients with kidney insufficiency using peritoneal dialysis , without any complications obtd. from the osmotic effect. The solns. correct the electrolyte bal the acid base bal.,achieve a sufficiently high removal of water and urine substances and are also nutritive for the patients. The solns. are simple to produce and use

Abstract (Equivalent): DE 3940052 C

Aq. dialysis and wash solns. for intraperitoneal use contain electrolytes, other osmotically active substances and opt. other additives giving a total osmotic pressure of 300-700 (320-550) m osm/l. The solns. contain a mixt. of alpha ketoacids in a total concn. of 1-70 (7.5-20)g/l.

The alpha ketoacids comprise 0-45 wt. pt. alpha ketoglutarate; 0-45 wt. pt. pyruvate; 0-45 wt. pt. alpha keto succinate; 6-9 wt. pt. 3-methyl-alpha keto valerate (I); 9-13.5 wt. pt. 4-methyl-alpha keto valerate (II); 0-9.5 wt. pt. 3-phenyl pyruvate; 13.5-20.5 wt. pt. 3-methyl-alpha-keto butyrate (III) 0-10 wt. pt. alpha-keto adipate; and 0-10 wt. pt. alpha-keto butyrate.

The amt. of (III) is more than that of (II), and the amt. of (II) is more than that of (I), pref. 2.25:1.5:1.

USE/ADVANTAGE - For patients with renal insufficiency etc.. Reduces the amt. of glucose etc. required in the soln..

Abstract (Equivalent): EP 431465 B

Aqueous dialysing and rinsing solution for intraperitoneal administration, containing electrolytes and additional osmotically active substances, optionally other additives, in which the total osmotic pressure is in the range of 300 to 700 mosm/l, characterised in that a mixture of the following components based on alpha-ketoacids in a (total) concentration of 1 to 70 g/l, the components are present in the following relative amounts: alpha-Ketoglutarate 0 to 45 parts by weight; Pyruvate (alpha-ketopropionate) 0 to 45 parts by weight; alpha-Ketosuccinate 0 to 45 parts by weight; 3-Methyl-alpha-ketovalerate 6 to 9 parts by weight; 4-Methyl-alpha-ketovalerate 9 to 13.5 parts by weight; 3-Phenylpyruvate 0 to 9.5 parts by weight; 3-Methyl-alpha-ketobutyrate 13.5 to 20.5 parts by weight; alpha-Ketoadipate 0 to 10 parts by weight; alpha-Ketobutyrate 0 to 10 parts by weight; and in which the ratio of the alpha ketoacids 3-methyl-alpha-ketobutyrate; 4-methyl-alpha-ketovalerate: 3-methyl-alphaketovalerate is preferably 2.25:1.5:1.

Dwg.0/0

Derwent Class: B05; P34

International Patent Class (Main): A61K-033/00

International Patent Class (Additional): A61K-031/19; A61M-001/28; A61K-031-19; A61K-031-195; A61K-031-70; A61K-033/00

14/7/10

008397426
WPI Acc No: 1990-284427/199038
Use of dimercapto -succinic acid to reduce blood or tissue silicon - thereby reducing blood pressure and improving renal function, or dementia
Patent Assignee: CEDARS SINAI MEDICAL CENT (CEDA-N); CEDARS-SINAI MED CE (CEDA-N); CEDARS SINAI MEDICAL CENTER (CEDA-N)
Inventor: GONICK H C; KHALIL-MANESH F; WEILER E W J; KHALILMANE F; WEILLER E W J
Number of Countries: 021 Number of Patents: 013
Patent Family:

| Patent No | Kind | Date | Applicat No | Kind | Date | Week | |
|---|---|---|---|---|---|---|---|
| EP 388241 | A | 19900919 | EP 90302905 | A | 19900319 | 199038 | B |
| US 4962127 | A | 19901009 | US 89325297 | A | 19890317 | 199043 | |
| PT 93462 | A | 19901107 | | | | 199047 | |
| AU 9051325 | A | 19901108 | | | | 199101 | |
| JP 3007219 | A | 19910114 | JP 9068003 | A | 19900317 | 199108 | |
| CA 2012091 | A | 19910913 | | | | 199148 | N |
| CA 2012470 | A | 19910919 | | | | 199149 | N |
| KR 9206904 | B1 | 19920822 | KR 903618 | A | 19900317 | 199406 | |
| EP 388241 | B1 | 19950125 | EP 90302905 | A | 19900319 | 199508 | |
| DE 69016232 | E | 19950309 | DE 616232 | A | 19900319 | 199515 | |
| | | | EP 90302905 | A | 19900319 | | |
| JP 95029917 | B2 | 19950405 | JP 9068003 | A | 19900317 | 199518 | |
| CA 2012470 | C | 19951107 | CA 2012470 | A | 19900319 | 199604 | N |
| IE 66237 | B | 19951213 | IE 901021 | A | 19900320 | 199608 | |

Priority Applications (No Type Date): US 89325297 A 19890317
Cited Patents: 7.Jnl.Ref
Patent Details:

| Patent No | Kind | Lan | Pg | Main IPC | Filing Notes |
|---|---|---|---|---|---|
| EP 388241 | A | | | | |
| Designated States (Regional): AT BE CH DE ES FR GB GR IT LI LU NL SE | | | | | |
| EP 388241 | B1 | E | 13 | | |
| Designated States (Regional): AT BE CH DE DK ES FR GB GR IT LI LU NL SE | | | | | |
| DE 69016232 | E | | | | Based on patent EP 388241 |
| JP 95029917 | B2 | | 8 | | Based on patent JP 3007219 |

Abstract (Basic): EP 388241 A
Use of dimercaptosuccinic acid (DMSA) for reducing blood or tissue silicon levels in humans and animals.
USE/ADVANTAGE - Redn. of silicon levels with DMSA is useful for reducing blood pressure and for improving renal function, also for the treatment of chronic renal failure, Alzheimer's disease, and senile dementia. claimed, in the treatment of kidney disease, a DMSA-silicon complex is formed, which is removable by a dialytic process e.g. hemodialysis, peritoneal dialysis , hemofiltration, or charcoal or resin perfusion. Admin. is oral or parenteral; pref. human daily dose is 10-30 mg/kg. In contrast to 2,3- dimercaptopropanol (BAL) an antidote for metal poisoning, DMSA is less toxic, has greater water solubility, limited lipid solubility, and is effective orally. To date there are no known chelating agents effective for silicon removal and no previously demonstrated effects of silicon removal. Glomerular filtration rates and blood pressure in DMSA-treated rats are restored to the same levels as in young animals due to reduction in silicon. (10pp Dwg.No.0/2)
Abstract (Equivalent): EP 388241 B
Use of dimercaptosuccinic acid (DMSA) in the manufacture of a

medicament for use in reducing the level of silicon in blood.
(Dwg.0/2

Abstract (Equivalent): US 4962127 A

Silicon levels in the blood or tissue of humans or other animals, comprises admin. of an effective amt. of dimercaptosuccinic acid, pref. by oral or parenteral admin..

USE/ADVANTAGE - Process is used to reduce blood pressure, improve kidney function, prevent or retard progress of chronic renal failure, treat the accumulation of Si in advanced kidney disease, and/or prevent the onset or improve the current status of dementia and Alzheimer's disease. (8pp

Derwent Class: B05; P34

International Patent Class (Main): A61K-031/19

International Patent Class (Additional): A61U-031/18

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